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AMERICAN JOURNAL OF

DISEASES of CHILDREN

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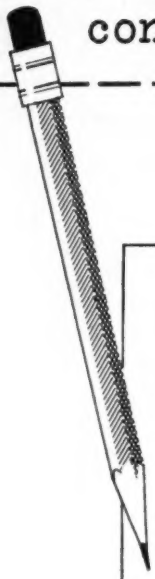

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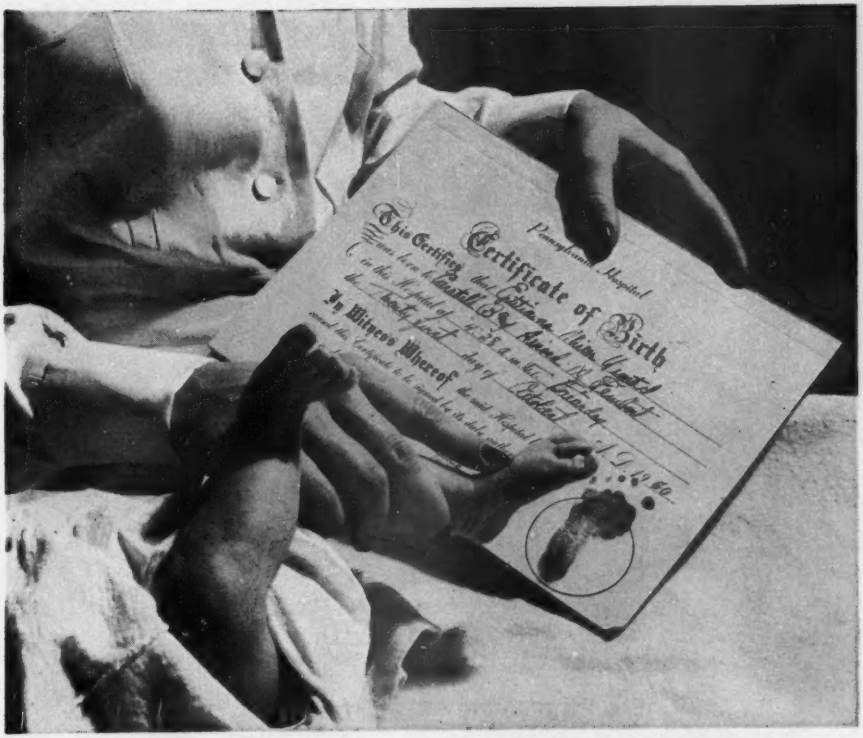

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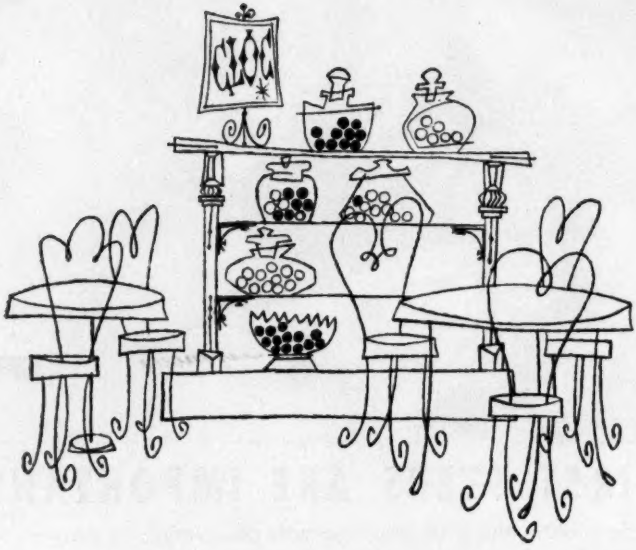

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*McClure, F. J.: Fluorine in Foods, Public Health Reports, 64:1061; 1949.

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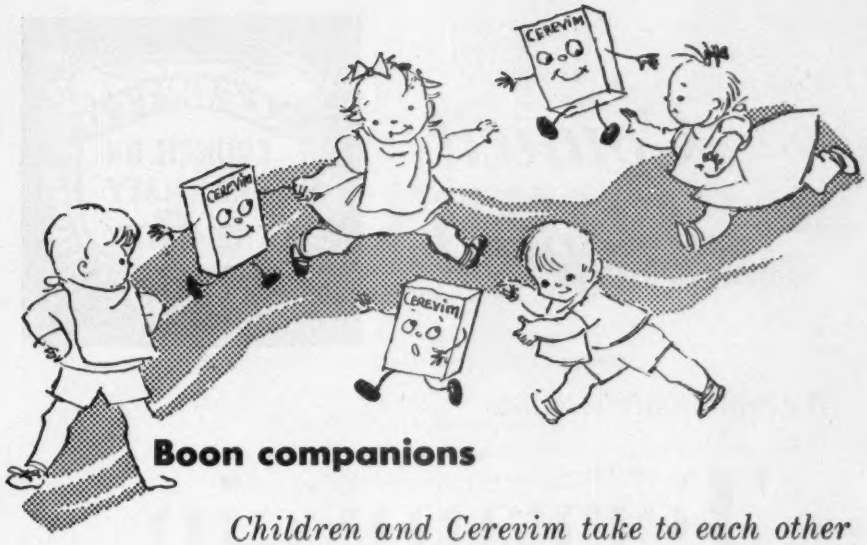

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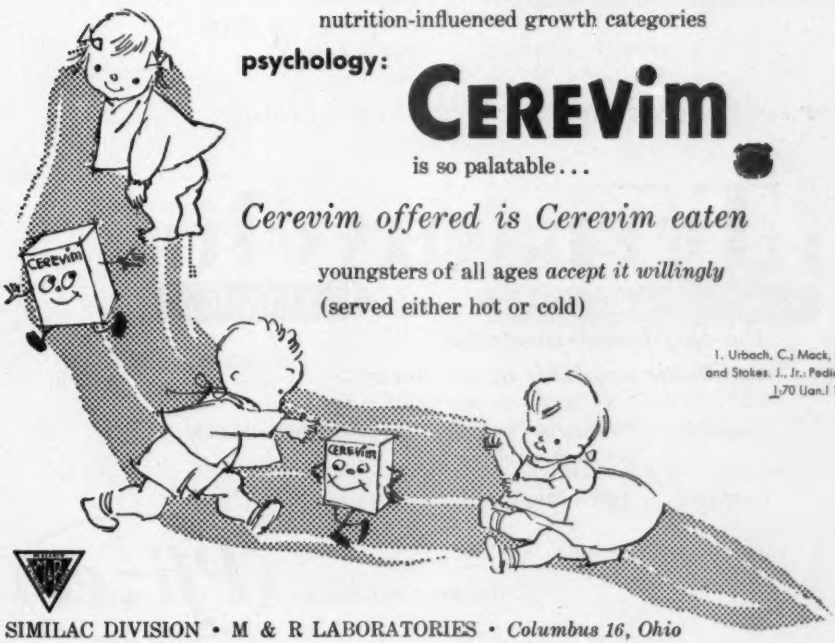

1. Urbach, C.; Mack, P. B., and Stokes, J., Jr.: Pediatrics 1:70 (Jan.) 1948.

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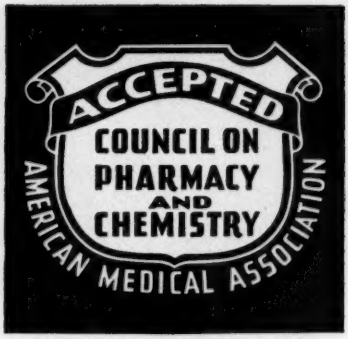

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J. V. Cooke in Brennemann's Practice of Pediatrics, Vol. 4, Chap. 41.

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A. M. A.
American Journal of Diseases of Children

VOLUME 81 MAY 1951 NUMBER 5

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RETROLENTAL FIBROPLASIA

The Role of Hemorrhage in Its Pathogenesis

WILLIAM E. LAUPUS, M.D.
AND
FRANKLYN P. BOUSQUET Jr., M.D.
NEW YORK

A STUDY was undertaken to evaluate the role of vitamin E in prophylaxis of retrolental fibroplasia. Serial ophthalmoscopic examinations thus far made on 72 premature infants weighing less than 1,650 Gm. at birth have established the importance of hemorrhage, an unexpected finding, as a precursor of the fully developed disease. Previously retinal hemorrhages have been described only in isolated case reports and have not been given sufficient emphasis in pathogenesis.

METHODS

All infants weighing less than 1,650 Gm. on admission to the nursery for premature infants of the New York Hospital–Cornell Medical Center were given routine ophthalmoscopic examinations. The initial examination was usually made prior to the removal of the infant from the incubator, and subsequent examinations were carried out at weekly intervals during hospitalization. After discharge periodic examinations were made in a special follow-up clinic. For infants over 6 months of age, when indicated, examination was performed with the infant under anesthesia.

Full mydriasis was obtained with 1 per cent homatropine hydrobromide solution in combination with 2.5 per cent buffered ophthalmic phenylephrine (neo-synephrine®) hydrochloride solution. Excellent cooperation was obtained from the infants by means of a standard rubber nipple stuffed with cotton saturated with 5 per cent dextrose solution. All examinations were carried out by one of us, and abnormalities, when observed, were confirmed by both of us and, when indicated, by other members of the department of ophthalmology.

On admission to the nursery for premature infants, all infants were routinely placed in an incubator, usually of the Gordon Armstrong or Isolette types. Use of the incubator, with constant temperature and humidity regulation and high oxygen concentration, was maintained until the infants weighed 1,500 Gm. or demonstrated no further need for its continuance.

After an initial fasting period of 12 to 24 hours the infants were given small feedings of 5 per cent dextrose solution at intervals of three hours for the next 12 hours. Thereafter, all infants received a formula consisting of diluted powdered partially skimmed cow's milk reenforced with dextri-maltose®.[1] Shortly before discharge a standard dilution of evaporated milk with added dextri-maltose® was substituted for the above formula.

All infants were routinely given 4 mg. of vitamin K (menadione) intramuscularly on admission. Administration of ascorbic acid orally, 50 mg. daily, was usually begun on the seventh or

This study was supported in part by a grant from the Playtex Park Research Institute.

From the New York Hospital–Cornell Medical Center, Departments of Pediatrics and Surgery (Ophthalmology).

Read in part before the Section on Pediatrics of the New York Academy of Medicine on Dec. 14, 1950 and before the Eastern Division of the Association for Research in Ophthalmology on Jan. 27, 1951.

1. Gordon, H. H.; Levine, S. Z., and McNamara, H.: Feeding of Premature Infants: Comparison of Human and Cow's Milk, Am. J. Dis. Child. **73**:442 (April) 1947.

eighth day of life. Alternate infants received a water-soluble vitamin D preparation, calciferol (drisdol®); the other infants were given vitamins A and D in an alcohol base.

In addition, all except two infants received vitamin E, 50 mg., three times daily. Sixty-five infants were given an aqueous dispersion of *dl*-alpha-tocopherol acetate [2] commencing with the first feeding. The other five infants received *dl*-alpha-tocopherol acetate (ephynal® acetate) beginning with the first sign of fundus abnormality. This medication was continued until examinations had conclusively shown the fundus to be normal or to have consistent irreversible pathologic changes. High serum tocopherol levels were found in all instances when the determination was made. None of the infants received supplemental iron in any form. Blood transfusions were given when indicated by anemia.

RESULTS

Of 72 infants under observation, 56 showed normal fundi on the initial examination and 27 continued to exhibit normal findings on all subsequent examinations. The normal fundus of the premature infant differs from the normal adult fundus in three major respects: 1. The optic disk presents a homogeneous pallor. 2. The foveal region and, particularly, the macula appear underdeveloped, being differentiated mainly by location and by a deeper red color from the surrounding retina. 3. The periphery of the retina consistently demonstrates a sharply demarcated pale gray or white zone, a finding most marked in dark-complexioned infants.

Residual Pathological Involvement of Eyes

Infant	Sex	Birth Weight, Gm.	Eye Involved	Result
L. S.	M	860	Both	Retrolental fibroplasia
J. V.	M	1,020	Both	Retrolental fibroplasia
D. M.*	F	1,320	Both	Retrolental fibroplasia
O. M.*	M	1,320	Both	Retrolental fibroplasia
E. T.	F	1,361	Both	Retrolental fibroplasia
J. C.	M	1,417	Both	Retrolental fibroplasia
D. O.*	M	1,410	Both	Severe retinal detachments
F. D.*	M	1,420	Both	Severe retinal detachments
S. F.	F	1,530	Both	Severe retinal detachments
G. A.*	F	1,080	Both	Temporal retinal detachments
L. D.*	F	1,320	Both	Temporal retinal detachments
B. J.*	F	1,440	Both	Temporal retinal detachments
G. S.	F	900	Right	Normal
			Left	Temporal retinal detachment
C. C.	F	1,100	Right	Normal
			Left	Temporal retinal detachment

* These infants received pituitary adrenocorticotropic hormone (ACTH) in doses ranging from 12.5 to 50 mg. daily for periods varying from seven to 28 days.

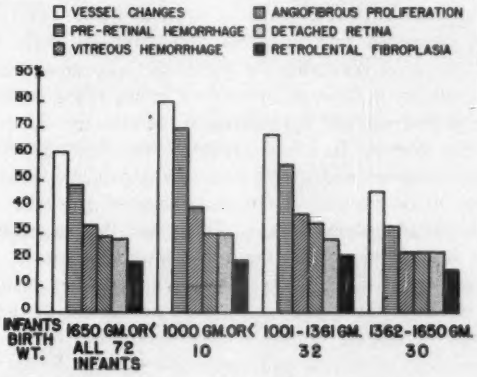
Sixteen infants showed venous caliber increase and arterial tortuosity of the retinal vessels on the first examination. In addition, three of these 16 infants had preretinal or vitreous hemorrhages. Venous caliber increase and venous and arterial tortuosity were later demonstrated in an additional 28 infants.

These early signs of vascular abnormality were followed in 34 of the 44 infants by preretinal hemorrhages, and in 23, by extension of the preretinal hemorrhage into the vitreous. Only one infant showed hemorrhage formation without antecedent vessel changes. In 15 of these 35 infants, 11 with uncomplicated preretinal hemorrhage and 4 with hemorrhagic extensions into the vitreous, no further progression of the disease was seen and the retinas returned to normal.

2. The aqueous dispersion of *dl*-alpha-tocopherol acetate was supplied by Hoffmann-LaRoche, Inc., Nutley, N. J.

In the remaining 20 infants replacement of the preretinal or vitreous hemorrhages by angiofibrous proliferation and neovascularization developed, and in 18 retinal detachment resulted at the site of these changes. In only one infant [3] were these changes observed without antecedent hemorrhage. Significantly, these detachments were located at the transition zone between the normal-appearing central portion of the retina and the pale periphery in 14 of these 19 infants.[4] The retina returned to normal in only five of the 19 infants. In the other 14 there was progression to retrolental fibroplasia in its complete or arrested form, as shown in the table.

Complete bilateral retrolental membranes, formed by fusion of the folds of completely detached retina behind the posterior surface of the lens, were seen in six infants. Of these, five had previously shown multiple areas of retinal detachment and diffuse clouding of the vitreous as prominent features of the disease. The other eight infants showed arrest of the process at the stage of severe retinal detachment and were left with permanent detachments as residuals of the disease.



Relation of fundus changes to birth weight.

The figure demonstrates the incidence of the progressive stages of fundus abnormality in the total group of 72 infants. For illustrative purposes, an arbitrary division of these 72 infants into three groups based on birth weight has been made, and the relative incidence is charted for each group.

In the over-all group, vessel changes were observed in 61 per cent of the infants and preretinal hemorrhages were seen in 48.6 per cent. The subsequent stages occurred with gradually decreasing frequency until in 19.4 per cent of the infants complete or partial retrolental fibroplasia developed.

As expected, the incidence of all changes was greatest in the infants of lowest and intermediate birth weight. The occurrence of retrolental fibroplasia was

3. This infant had shown marked vessel changes while in the hospital. A period of 18 days elapsed before the next examination, which showed neovascularization, angiofibrous proliferation and early retinal detachment.

4. Far peripheral sector elevation of the retina was incidentally observed in three infants with otherwise normal retinas. In each instance on subsequent examination the retina was entirely normal. These transient retinal elevations were not considered to be a part of the disease.

approximately the same in all weight groups, but the number of infants studied is still too small for these figures to have statistical significance.

Neither persistence of the hyaloid artery-tunica vasculosa lentis system nor retinal exudation was observed at any of our examinations.

Evidences of bleeding into the skin, the subcutaneous tissues and the visceral organs were not found in any infants. Fourteen determinations of the prothrombin time in 11 of the 35 infants with intraocular hemorrhage gave values ranging from 64 to more than 100 per cent of adult normal values. Thrombocyte (platelet) counts for the same infants were within similar limits.

The late sequelae,[5] including such secondary changes as microphthalmos, posterior synechias, shallow or flat anterior chambers and glaucoma, were observed in many of our infants in whom retrolental fibroplasia developed, but their detailed discussion is outside the scope of this report.

COMMENT

The concept that postnatal intraocular hemorrhage plays an important role in the development of retrolental fibroplasia is not a new one. Terry,[6] citing one of Goldberg's cases, suggested that intraocular hemorrhage might be significantly implicated. However, after reviewing the pathologic specimens available for study, he rejected this possibility in favor of a persistent tunica vasculosa lentis. Reese and Payne [7] discussed persistence and hyperplasia of the primary vitreous in relation to the causation of this disease. In a later report Reese [8] separated retrolental fibroplasia from true persistence and hyperplasia of the primary vitreous. The latter author, in writing of the relation of the persistence of a portion of the primary vitreous to retrolental fibroplasia, states: "It is from this vascular tissue that the hemorrhages and subsequent organization and contraction stem."

The original concept that retrolental fibroplasia stems from either a congenital arrest of normal development of the eye or from persistence of embryologic structures which normally disappear is readily understood when one recalls that it was formulated on the basis of clinical and pathologic signs observed in cases of the fully developed disease.

Earlier and more frequent ophthalmoscopic examinations have led more recent observers to postulate a postnatal genesis for the disease, the condition resulting from the physiologic handicaps peculiar to premature infants [9] or from the artificial measures employed to preserve their lives.

The work of Owens and Owens [10] conclusively demonstrated that the eye of the premature infant can be examined satisfactorily and repeatedly without resort to

5. King, M. J.: Retrolental Fibroplasia: A Clinical Study of 238 Cases, Arch. Ophth. **43**:694 (April) 1950.

6. Terry, T. L.: Fibroblastic Overgrowth of Persistent Tunica Vasculosa Lentis in Premature Infants: IV. Etiologic Factors, Arch. Ophth. **29**:54 (Jan.) 1943.

7. Reese, A. B., and Payne, F.: Persistence and Hyperplasia of the Primary Vitreous (Tunica Vasculosa Lentis or Retrolental Fibroplasia), Am. J. Ophth. **29**:1 (Jan.) 1946.

8. Reese, A. B.: Persistence and Hyperplasia of Primary Vitreous: Retrolental Fibroplasia, 2 Entities, Arch. Ophth. **41**:527 (May) 1949.

9. Levine, S. Z., and Gordon, H. H.: Physiologic Handicaps of the Premature Infant: Their Pathogenesis, Am. J. Dis. Child. **64**:274 (Aug.) 1942.

10. Owens, W. C., and Owens, E. U.: Retrolental Fibroplasia in Premature Infants, Am. J. Ophth. **32**:1 (Jan.) 1949.

anesthesia and special devices. Persistence of the tunica vasculosa lentis and of the hyaloid artery system was not seen by them in nine infants in whom retrolental fibroplasia developed. Venous dilatation and arterial tortuosity were present in all cases, and hemorrhage was noted in three cases; however, hemorrhage was seen only after the retrolental mass had formed. They concluded that in this disease

> . . . the initially normal fundus picture was replaced by an angiomatous dilatation of the retinal vessels, followed by massive retinal exudation, retinal detachment, and the formation of a retrolental membrane by fusion of the peripheral folds of detached retina.

Gilger [11] recently reported on three patients followed from birth to the appearance of retrolental fibroplasia. Hemorrhages, probably indicative of "some vascular disorder," were noted on the surface of retinal detachments early in the course of the disease process.

Unsworth,[12] in a preliminary report, described vessel changes, preretinal hemorrhages, leakage of blood into the vitreous and organization of the hemorrhage into the vitreous by vascularization from the retinal vessels in a small premature infant. He ascribed all these changes to a preexisting abnormality of the vitreous.

The consistent pattern of abnormal ophthalmologic observations, as determined by serial examination in our infants, permits an arbitrary division of the pathogenesis of retrolental fibroplasia into six stages:

1. A vascular stage consisting of arterial and venous tortuosity of the retinal vessels with increased caliber of the veins

2. A hemorrhagic stage with rupture of the retinal vessels, leading to the formation of preretinal or subhyaloid hemorrhages

3. A stage of extension, in many instances, of the preretinal hemorrhage into the vitreous

4. A stage of organization of the hemorrhages with angiofibrous proliferation, consisting of the formation of fibrous bands and neovascularization

5. The stage of retinal detachment, usually at the zone of transition between the normal-appearing central and the pale peripheral portion of the retina, a site where preretinal hemorrhage and subsequent angiofibrous proliferation appear to have the most serious prognostic importance

6. The final stage of fully developed retrolental fibroplasia with retrolental membranes formed by fusion of the peripheral folds of detached retina and adherence of the detached retina to the posterior surface of the lens

The disease process in its different stages resembled, in many respects, retinitis proliferans or Coats's disease (retinitis exudativa) in adults, although the time span is much shorter than that observed in the adult disease.

The potential reversibility of the disease, with subsequent regression to the normal fundus, at any stage short of severe retinal detachment is indicated by the decline in incidence of the progressive stages. When the process halts at the stage of retinal detachment, a less severe form of the disease results.

Organization of preretinal and vitreous hemorrhages with subsequent development of retinal detachment fits well into the microscopic pathologic changes of

11. Gilger, A. P.: Retrolental Fibroplasia in Prematurely Born Children, Am. J. Ophth. **32**:917 (July) 1949.

12. Unsworth, A. C.: Retrolental Fibroplasia: A Preliminary Report, Arch. Ophth. **40**:341 (Sept.) 1948.

retrolental fibroplasia as described by Terry,[13] Reese,[14] Klien [15] and others. The most frequent origin of fibrous tissue in the vitreous in other age groups is organization of hemorrhage. Premature infants are not exempt from this well known process.

Although the present study of the efficacy of vitamin E in the prophylaxis of this disease is not complete, the results to date are discouraging. Of the 65 infants receiving *dl*-alpha-tocopherol acetate, 50 mg. three times daily, commencing with the first feeding, in 11, or 17.0 per cent, retrolental fibroplasia developed in its partial or complete form. The disillusioning nature of these figures in the face of supranormal serum tocopherol levels is not in accord with the promising results attributed to vitamin E by Owens and Owens.[16] The absence of a comparable control series makes it impossible to state whether vitamin E modified the severity of the end result in any of our infants.

A number of questions remain unanswered: Is the vascular process limited to the retinal vessels? Why is the small premature infant more susceptible to retinal hemorrhage than the normal full term newborn or even the newborn with hemorrhagic disease?[17] What role, if any, do the newer techniques for preserving the lives of these premature infants play? Is the length of stay in the incubator, the oxygen concentration of the incubator air or the duration of oxygen therapy of importance? Does the diet, including vitamins other than vitamin E, have any relation to the disease?[18] Will pituitary adrenocorticotropic hormone (ACTH) live up to its early promise in therapy? Must retrolental fibroplasia be regarded as a necessary concomitant to the increased survial of the small premature infant? Some of these factors are presently under investigation.

SUMMARY

Serial ophthalmoscopic observations are reported on 72 premature infants weighing less than 1,650 Gm. at birth.

The features characterizing the normal premature fundus, especially the existence of a sharply defined pale peripheral zone of retina, are described.

The theory of postnatal development of retrolental fibroplasia is supported by the absence of serious ophthalmologic abnormalities from all our infants at the initial examination.

13. Terry, T. L.: Fibroblastic Overgrowth of Persistent Tunica Vasculosa Lentis in Premature Infants: II. Report of Cases; Clinical Aspects, Arch. Ophth. **29**:36 (Jan.) 1943.

14. Reese and Payne.[7] Reese.[8]

15. Klien, B. A.: Histopathologic Aspects of Retrolental Fibroplasia, Arch. Ophth. **41**:553 (May) 1949.

16. Owens, W. C., and Owens, E. U.: Retrolental Fibroplasia in Premature Infants: Studies on the Prophylaxis of the Disease; the Use of Alpha-Tocopherol Acetate, Am. J. Ophth. **32**:1631 (Dec.) 1949.

17. Maumanee, A. E.; Hellman, L. M., and Shettles, L. B.: Factors Influencing Plasma Prothrombin in the Newborn Infant: The Effect of Antenatal Administration of Vitamin K on the Incidence of Retinal Hemorrhages in the Newborn, Bull. Johns Hopkins Hosp. **68**:158 (Feb.) 1941.

18. Kinsey, V. E., and Zacharias, L.: Retrolental Fibroplasia: Incidence in Different Localities in Recent Years and Correlation of Incidence with Treatment Given Infants, J. A. M. A. **139**:572 (Feb. 26) 1949.

In 13 of 14 infants in whom retrolental fibroplasia developed, a consistent pattern of pathogenesis from the first stage of minimal retinal vessel changes through each of five succeeding stages, preretinal hemorrhage formation, extension of these hemorrhages into the vitreous, organization of the hemorrhages with angiofibrous proliferation, subsequent retinal detachment and the formation of a retrolental membrane, has been observed.

Special emphasis is placed on preretinal hemorrhage as a necessary precursor of the succeeding stages of retrolental fibroplasia.

The potential reversibility of the developing retrolental process at any stage short of severe retinal detachment is noted.

The high incidence of serious ophthalmologic abnormalities, despite supplementation with vitamin E, challenges the prophylactic role attributed to the tocopherols in treatment of this disease.

CONCLUSION

Postnatal intraocular hemorrhages are common in small premature infants, and retrolental fibroplasia is a sequel to these hemorrhages.

REPORT OF CASES

CASE 1.—J. C., a white boy, weighing 1,040 Gm., was born by breech extraction on Jan. 12, 1950, about eight weeks before term. His male twin died shortly after birth. The neonatal period was complicated by respiratory difficulty and mild diarrhea, but his subsequent hospital course was entirely normal. Administration of vitamin E was begun with the first feeding and was continued to the age of 5 months.

Ophthalmoscopic Examinations.—1. Age, 37 Days: The anterior segment of the right eye was normal. The vitreous was clear, and the disk was pale but otherwise normal. The retinal vessels showed increased caliber of the veins and rather marked tortuosity of both arteries and veins. The far peripheral portion of the retina was a pale gray-white, and a large preretinal hemorrhage was noted in the inferotemporal quadrant near the periphery. The retina was otherwise normal. The ophthalmoscopic observations for the left eye, except for the absence of hemorrhage, were similar to those for the right eye.

2. Age, 43 Days: The examination was unsatisfactory because of poor dilatation. In the right eye the venous caliber increase and arterial and venous tortuosity were more pronounced. A new small superficial preretinal hemorrhage was found adjacent to the midportion of the superior temporal artery. The previously described large inferotemporal hemorrhage could not be seen, presumably owing to the poor dilatation. In the left eye the vessel changes were similarly increased. A new small preretinal hemorrhage was seen just below the disk, and a similar hemorrhage was present along the distal portion of the superior temporal artery.

3. Age, 50 Days: The vessel changes were very conspicuous in the right eye. The previously noted inferotemporal hemorrhage was larger and occupied much of the inferotemporal periphery. Immediately beyond this hemorrhage, the peripheral portion of the retina was sharply elevated to + 6 D. Vessel changes in the left eye were similar to those in the right. The hemorrhage in the superior temporal quadrant was larger and exhibited new extensions into the vitreous. The retina was normal except for questionable far peripheral elevation.

4. Age, 51 Days: In the right eye a portion of the inferotemporal hemorrhage extended into the vitreous; there were no other new developments. In the left eye several small areas of fine neovascularization were seen about the superotemporal hemorrhage. Peripheral to this hemorrhage, the retina was sharply tented and elevated to + 10 D. Three small new hemorrhages were present on the surface of this elevation.

5. Age, 57 Days: In the right eye the vessel changes had regressed slightly. The inferotemporal hemorrhage was a red-brown and sent numerous small angiofibrous extensions into the vitreous. The peripheral detachment had extended superiorly and inferiorly and was more sharply elevated (to + 20 D.) and was seen closely adjacent to the posterior surface of the lens. A new

large hemorrhage was present on the surface of the detachment. Similar, though less marked, changes were present in the left eye. The superotemporal hemorrhage appeared to be organizing with angiofibrous extensions into the vitreous. The detachment had extended inferiorly, and the three small hemorrhages on its surface appeared to have coalesced, forming a single large hemorrhage.

6. Age, 59 Days: The detachment had extended superiorly, inferiorly and nasally in the right eye, and a new preretinal hemorrhage was noted in the macular area. Other findings were unchanged. In the left eye the detachment had extended slightly inferiorly and superiorly.

7. Age, 62 Days: No changes from the previous examination were noted in the right eye. In the left eye a delicate neovascular network was present around and on the disk. The detachment had advanced anteriorly until it approached the posterior surface of the lens.

8. Age, 64 Days: A neovascular network was noted on and around the disk of the right eye. The detachment of the retina extended to all quadrants, sparing only the macular region. Fibrous bands containing vessels were clearly visible in the area of original detachment in the inferotemporal periphery. In the left eye fibrous bands containing vessels, similar to those in the right eye, were seen in the superior temporal periphery. The neovascular network on the disk was more extensive, but the detachment was unchanged.

9. Age, 70 Days: In the right eye a new hemorrhage was seen on the peripheral surface of the detachment at about 5 o'clock. In the left eye there were no changes from the previous examination.

10. Age, 75 Days: In the right eye the vascular changes had further regressed. The retina had settled considerably since the last examination and was elevated to only + 8 D. in the temporal periphery. The neovascularization remained on the disk, and the hemorrhage on the surface of the detachment extended into the vitreous. The temporal detachment had regressed in the left eye, especially inferiorly. The neovascularization on the disk and the hemorrhage on the detached superotemporal portion of the retina were still seen.

11. Age, 92 Days: The vessel changes were markedly decreased in the right eye. The disk no longer showed the earlier surface neovascularization. The inferotemporal portion of the retina was still detached, with several large hemorrhages on its surface. A few dark strands extended into the vitreous in this region. In the left eye the temporal detachment consisted of a fold of elevated retina. From the inferior border of the fold several dark strands extended into the vitreous. The hemorrhages were seen peripheral to the fold, where the retina was again flat.

12. Age, 106 Days: In both eyes the vessels still showed slight but definite venous caliber increase and arterial tortuosity. The retinas were normal. In the temporal periphery of both eyes the thin dark strands extending into the vitreous remained as the only evidence of the previously described abnormalities.

13. Age, 127 Days: In both eyes the dark strands in the vitreous were still present but were more peripheral than on previous examinations.

14. Age, 155 Days: In both eyes the ophthalmoscopic observations remained unchanged.

15. Age, 222 Days: In both eyes examination showed normal findings. The strands extending into the vitreous were no longer present.

16. Age, 255 Days: Ophthalmoscopy, with the patient under anesthesia, failed to reveal any abnormalities in either eye.

CASE 2.—O. M., a white boy, weighing 1,320 Gm., was born on April 29, 1950 after a normal pregnancy terminated at 32 weeks by premature onset of labor. The immediate neonatal period was complicated by mild atelectasis. The rest of the hospital course was uneventful. Administration of vitamin E was begun with the first feeding and, except for an unavoidable lapse of three weeks at 3½ months of age, was continued until the infant was 5½ months old. Pituitary adrenocorticotropic hormone (ACTH), 50 mg. daily, was given for a period of one week at the age of 2 months.

Ophthalmoscopic Examinations.—1. Age, 26 Days: In both eyes the anterior segment was normal, the vitreous was clear and the disk was pale but otherwise normal. The retinal vessels showed mild venous caliber increase and arterial tortuosity, and the retinas were normal.

2. Age, 34 Days: In the right eye the venous caliber and arterial tortuosity were markedly increased. Two small preretinal hemorrhages were seen above the macular region. A larger preretinal hemorrhage was located at 9 o'clock in the temporal periphery. Vascular abnormalities in the left eye were similar to those in the right eye. No hemorrhages were present.

3. Age, 41 Days: The vessel changes were severer in the right eye. The preretinal hemorrhages above the macula and in the temporal periphery were smaller. In the left eye several small preretinal hemorrhages were present above the nasal margin of the disk.

4. Age, 48 Days: In the right eye the preretinal hemorrhages above the macular region extended into the vitreous; the retina was normal. In the left eye a new preretinal hemorrhage was noted from 2 to 3 o'clock in the temporal periphery.

5. Age, 58 Days: The previously described hemorrhages in the right eye were barely visible, and the retina was normal. In the left eye as in the right, the vessel abnormalities, were still severe. A crescent-shaped fold of retina, elevated + 3 D., was located at the transition zone between the central portion of the retina and the pale periphery from 1 to 8 o'clock. The part of the retina peripheral to the fold appeared slightly elevated. The previously noted preretinal hemorrhage overlay the retinal fold at 2 to 3 o'clock. Wispy, veil-like, partially fibrous extensions into the vitreous arose from the hemorrhage at 2 o'clock and from a neovascular base at 3 o'clock, where the hemorrhage was seen on the last examination. Similar wispy extensions into the vitreous were located at 6 o'clock on the margin of the fold. The remainder of the retina was normal.

6. Age, 59 Days: In the right eye the hemorrhages above the macular region were not visualized, but at their former site there was a horizontal, crescentic, slightly elevated fold of retina. The edge of this fold showed many new vessels. Peripheral to the fold, the retina was detached and elevated + 5 D. In the left eye the retinal fold was unchanged. A thick dark strand, seemingly arising from a dilated and tortuous inferior temporal vein, extended into the vitreous at the nasal margin of the fold at 8 o'clock. The strand divided into several thin threads which coursed upward through the vitreous toward the posterior surface of the lens.

7. Age, 60 Days: The retinal fold in the right eye had extended circumferentially along the transition zone between the central and the pale peripheral parts of the retina from 8 to 11 o'clock. The surface neovascularization on the margin of the fold had increased. In the left eye there were no changes.

8. Age, 61 Days: ACTH therapy was begun at 61 days. In the right eye the retinal fold had increased inferiorly and extended from 5 to 1 o'clock. In the left eye there were no changes.

9. Age, 62 Days: In both eyes the vascular changes, especially the fulness of the veins, were slightly decreased.

10. Age, 63 Days: In both eyes more neovascularization was present on the surface of the sharply elevated folds, but the other abnormalities were unchanged.

11. Age, 64 Days: The nasal peripheral portion of the retina was slightly elevated in the right eye. In the left eye there were no essential changes.

12. Age, 65 Days: In both eyes the vessel changes had begun to show regression toward normal.

13. Age, 66 Days: The right eye showed no change. In the left eye during the previous week the areas of extension into the vitreous at 2 and 6 o'clock on the margin of the retinal fold had increased in size and elevation, and had gradually assumed the appearance of fibrous sheets, elevated to + 12 D. and + 8 D. within the vitreous. The remainder of the fold was less elevated. A dark strand extended between the fibrous areas, and fine dark fibrils extended from the inferior margin of this strand to the upper surface of the retinal fold.

14. Age, 67 Days: The neovascularization on the superior edge of the retinal fold of the right eye was denser, appearing as a thin white sheet extending into the vitreous above the margin of the fold. The left eye showed no changes.

15. Age, 68 Days: ACTH therapy was completed at 68 days. There were no changes in either eye.

16. Age, 69 Days: The superior portion of the retinal fold of the right eye was denser, and the fold itself was becoming thicker and whiter. The superior and inferior temporal vessels were

elevated at the central margin of the fold. In the left eye the extensions into the vitreous at the 8 o'clock inferior nasal margin of the fold had become denser and whiter, extending into the vitreous to a greater degree. The other fibrous sheets at 2 and 6 o'clock were larger, and the whole retinal fold was more elevated than before.

17. Age, 71 Days: The right eye showed no changes; in the left eye the retinal fold was more elevated, and detachment of the retina peripheral to it was more apparent.

18. Age, 72 Days: No change was found in the right eye. In the left eye the retina was almost totally detached, and the disk was obscured by a fold of nasal retina. The superior, temporal and inferior parts of the retina were elevated and were near the posterior surface of the lens. The nasal portion of the retina was least elevated (+ 8 D.) and had a billowing surface. The detachment formed a funnel-shaped passage which narrowed to a small base at the posterior polar area.

19. Age, 73 Days: The superior fibrous sheet of the right eye had slowly increased in size, but the retinal fold had shown no change. In the left eye the "corridor" between the billowing folds of detached retina was narrowing.

20. Age, 74 Days: In the right eye a new angiofibrous strand extended into the vitreous from the temporal margin of the superior fibrous sheet, and small fibrillar extensions passed from the strand to the temporal surface of the retinal fold. No changes were observed for the left eye.

21. Age, 76 Days: The retinal fold of the right eye was gradually becoming more fibrous in appearance and was more elevated. In the left eye the central area between the folds of detached retina was a thin slit.

22. Age, 78 Days: The detachment in the right eye had increased to involve the entire periphery from 5 to 1 o'clock, and the temporal portion was near the posterior surface of the lens. No change had occurred in the left eye.

23. Age, 83 Days: The retina of the right eye had become totally detached and was near the posterior surface of the lens. The retina of the left eye covered the posterior surface of the lens, except in the center, where a tiny slit opened down to the posterior portion of the eye.

24. Age, 90 Days: In the right eye the folds of detached retina were coming together centrally, producing a funnel-shaped passage toward the disk. In the left eye the posterior surface of the lens had become covered completely by a gray-white membrane.

25. Age, 118 Days: In the right eye there had been slight regression of the detachment in the inferonasal quadrant where the retina was flatter, without landmarks or vessels. The remainder of the retina, from 5 to 1 o'clock, was at the posterior surface of the lens as a gray-white membrane covering the greater part of the posterior lens surface. The anterior chamber of the left eye was slightly shallow; otherwise, abnormalities remained unchanged.

26. Age, 137 Days: Through the peripheral margin of the fully dilated pupil, elongated ciliary processes were easily visible in both eyes. The retrolental membranes were unchanged.

27. Age, 193 Days: In both eyes the anterior chambers were slightly shallow, but tension was normal to finger palpation. The pupils dilated completely without evidence of synechias. The elongated ciliary processes were again visualized. The right eye showed an almost complete retrolental membrane, the inferonasal retinal periphery being spared. The left retrolental membrane was complete. Neither eye was microphthalmic.

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PSYCHOEDUCATIONAL STUDY OF CHILDREN BORN DEAF FOLLOWING MATERNAL RUBELLA IN PREGNANCY

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DURING the period 1939 to 1941, a series of observations was made by Dr. N. McAlister Gregg, of Australia, which has proved to be a new landmark in the investigation of congenital defects in infants. These observations concerned an entirely new variety of congenital cataract of dense nuclear type occurring in babies and differing from any of the previously reported morphological types both in appearance and in developmental opacity. In 1941 Gregg's report [1] of his study of 78 such cases among children of New South Wales revealed the singular fact that the mothers of these babies, with few exceptions, had suffered from an exanthematous disease during early pregnancy. This disease had been diagnosed as rubella. Gregg, himself, was at first inclined to doubt the accuracy of the diagnosis, since apparently such defects had only come to notice as late as 1939. However, in 1942 the exanthematous disease in question was definitely established as rubella by Swan and his co-workers in the course of an intensive study of congenital defects in infants following infectious diseases in the mother during pregnancy.[2]

From that time to the present reports of cases and investigations confirming the association between various congenital defects and maternal rubella have been made by workers in different parts of the world.[3] The main conclusions have been derived largely from Swan's investigations and are (1) that the commonest congenital defects found in infants of mothers with rubella during pregnancy are

1. Gregg, N. M.: Congenital Cataract Following German Measles in the Mother, Tr. Ophth. Soc. Australia **3**:35, 1941.

2. Swan, C.; Tostevin, A. L.; Moore, B.; Mayo, H., and Black, G. H. B.: Congenital Defects in Infants Following Infectious Diseases During Pregnancy, with Special Reference to Relationship Between German Measles and Cataract, Deaf-Mutism, Heart Disease, and Microcephaly, and to Period of Pregnancy in Which Occurrence of Rubella Is Followed by Congenital Abnormalities, M. J. Australia **2**:201, 1943. Swan, C.; Tostevin, A. L.; Mayo, H., and Black, G. H. B.: Further Observations on Congenital Defects in Infants Following Infectious Diseases During Pregnancy, with Special Reference to Rubella, ibid. **1**:409, 1944. Swan, C.; Tostevin, A. L., and Black, G. H. B.: Final Observations on Congenital Defects in Infants Following Infectious Diseases During Pregnancy, with Special Reference to Rubella, ibid. **2**:889, 1946.

3. Conte, W. R.; McCammon, C. S., and Christie, A.: Congenital Defects Following Maternal Rubella, Am. J. Dis. Child. **70**:301 (Nov.-Dec.) 1945. Bamatter, F.; Bourquin, J., and Wenger, A. F.: Embryopathie rebeolique: malformations congenitales multiples à la suite d'une rubeole au debut de la grossesse, Rev. oto-neuro-oftal. **21**:240, 1949. Alarcón, A. G.: Rubella as a Cause of Congenital Malformations, Am. J. Dis. Child. **78**:914 (Dec.) 1949. Borremans-Ponthiere, P., and Ferrant, M.: Embryopathie de la rubeole, Acta pædiat. belg. **3**:235, 1949.

microcephaly, ocular abnormalities, defective hearing and heart lesions; (2) that if such infection is contracted by the mother during the first two months of pregnancy, the chances of the child being born with congenital abnormalities are about 100 per cent; if during the third month, the chances of congenital defect fall to about 60 per cent; if during the fourth month, to about 50 per cent, and after this, the chances of congenital defect are extremely small, and (3) that no infectious disease occurring during pregnancy other than rubella serves as antecedent of the congenital defects described in his investigations.

It should be noted that Swan's two latter conclusions are not universally accepted at this time. Fox and Bortin,[4] in their Milwaukee survey, raise the question of the number of normal children born to mothers who had rubella during pregnancy. Their findings suggest that women who contract rubella during even the second month of pregnancy may yet have normal children. Further, Lande [5] has reported the common cold in five cases and virus influenza in one case as the most likely causative factors of various congenital defects closely resembling the postrubella syndrome. Future investigations will, no doubt, eventually clarify these important observations.

Another observation that has come to light since Gregg's original report has, however, proved of high validity. This concerns the striking incidence of congenital deafness associated with maternal rubella.[6] Carruthers [7] anticipates that as many as 50 per cent or more of the children studied in Australia will eventually be found to have defective hearing. This was not recognized in the very early investigations, since the children then under observation were too young for an adequate evaluation of their hearing status. The importance of this finding is of great diagnostic as well as prognostic value; for in many cases of very young children with defective hearing, seeming oddities of behavior are mistakenly attributed to mental defects. It is for this reason in particular that a diagnostic awareness of the high incidence of congenital hearing defects associated with maternal rubella becomes especially important. The sooner deafness is recognized, the sooner can the child's unique problems and educational needs be met. Time wasted in such cases is time irretrievably lost.

When the association between congenital deafness and maternal rubella became known to the educator in the field of the deaf, he had then to prepare to assume the responsibility for the care and education of such deaf children when they attained school age. His chief need in this endeavor was to ascertain whether these children deafened through maternal rubella might be found to present other problems in addition to deafness, and if so what these problems might be. The "problem" areas with which he was most concerned were behavior, intelligence and school achievement, acoustic patterns and general health.

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4. Fox, M. J., and Bortin, M. M.: Rubella in Pregnancy Causing Malformations in Newborn, J. A. M. A. **130**:568 (March 2) 1946.

5. Lande, L.: Congenital Malformations with Severe Damage to the Central Nervous System Due to Early Fetal Virus Infection, J. Pediat. **36**:625, 1950.

6. Clayton-Jones, E.: Rubella as a Cause of Congenital Deafness in England, Lancet **1**:56, 1947. Hiller, B.: Rubella Congenital Inner Ear Deafness in Tasmania, M. J. Australia **2**:277, 1949.

7. Carruthers, D. G.: Congenital Deaf-Mutism as a Sequela of a Rubella-Like Maternal Infection During Pregnancy, M. J. Australia **1**:315, 1945.

MATERIAL AND METHODS

In order to clarify these points, The Lexington School for the Deaf, a residential school for such children in New York city, instituted plans to conduct a study of the first two school years of a group of congenitally deaf children born to mothers infected with rubella during pregnancy. During the period 1946 to 1948, 16 such children had been admitted to this school. Their respective ages at the time of admission were within the range 3 years to 4 years 10 months. It is interesting to note that all but one of the children had been born during the year 1943—reportedly a year of high incidence of rubella—and that one was born in January 1944. Eleven had been born in New York state and one in each of the following states: New Jersey, Pennsylvania, Florida, Mississippi and Virginia. In all cases birth was reported to have been at full term, spontaneous and normal. In no case was there any other deafness in the families; nor did the histories disclose any etiological factor other than maternal rubella which might possibly account for the deafness in the children.

The periods of pregnancy during which rubella was contracted by the respective mothers of these children were stated by them to be as follows: first month in one case, second month in four cases and third month in 11 cases. Memory for more precise chronological data was too vague in most instances to be reliable. In each case, however, the diagnosis of rubella had been made by a physician.

Other defects found among the children on medical examination were cervical adenitis, five cases; ocular defects, nine cases (one of unilateral congenital cataract; four of abnormal retinal pigmentation; one of abnormal macular pigmentation; two of diffuse pigmentary degeneration; one of chorioretinitis); systolic murmur, seven cases; umbilical hernia, three cases; pigeon breast, two cases; enlarged spleen, one case; aphagia, one case; digestive disorder, one case; cryptorchism, one case. All but three of the children had one defect or more in addition to deafness. The most frequently occurring combinations were deafness and ocular abnormalities, in eight cases, and deafness and systolic murmur, in seven cases. Deafness, ocular abnormalities and systolic murmur occurred in four cases.

At the time of application for school admission preliminary observation of each applicant was made by the school principals with a view to class placement. Thirteen of the applicants appeared quite like other small deaf children in their general behavior and responsiveness to play and to people. None were feeding problems, and all had bladder and bowel control. The four boys and nine girls of this group were accordingly admitted into the regular nursery classes. The remaining three children—two boys and one girl—were, however, highly atypical in all their observed reactions. Their behavioral pictures appeared to combine infantile characteristics, defective mentality, inappropriate emotional responsiveness and queer motor mannerisms. None of the three had as yet established bowel or bladder control, and two had not yet learned to chew solid food. Their respective ages at this time were 3 years 8 months, 3 years 10 months and 4 years 8 months.

It was decided that, in spite of their evident abnormalities, the three would be admitted to school on an experimental basis to see what could be accomplished with them. Accordingly, a special class and program were organized under the supervision of a special class teacher and clinical psychologist. The goals of the program were set up in accordance with the observed behavioral needs of the children and centered about (1) bringing them into a state of awareness of and appropriate contact with their environment; (2) socialization; (3) training in daily habits; (4) training in manipulative skills, and (5), in general, "humanization."

During the course of the two succeeding years, psychological observations, the results of psychological and audiometric tests, teachers' reports, medical records and motion picture records of all 16 children were compiled for reference and analysis. At the conclusion of the study analysis of the reference materials was made and yielded the following findings.

BEHAVIOR

Regular Class Group.—The general behavior of the 13 children who had been admitted to the regular classes was found to be much the same as that of their deaf peers. The chief difference was a greater tendency to hyperactivity, tenseness and low stimulus threshold among the children deafened as a result of maternal rubella.

No evidences of emotional disturbance could be found to account for this, and histories showed presence of this pattern since early infancy. The degree of hyperactivity, while sufficient to be noteworthy, was not of such order as to interfere with either the children's school progress or their satisfactory adjustment.

Special Class Group.—The general behavior of the three special class children was strongly suggestive of some type of brain damage or disease. Unfortunately, members of the neurological clinic to which they had been referred could not carry out examinations on them because of their wild resistance and general panic reaction. For the same reason electroencephalograms could not be secured.

The following brief excerpts, selected from various reports, illustrate something of the behavior of the children:

PATIENT S. C. (rubella contracted by mother during second month of pregnancy).—This 5 year old boy had had cataract extraction and has poor vision. He prefers, when left to himself, to stretch out on the ground, crossing his legs and regarding his hands and fingers which he holds upraised above his eyes. Or else he will stiffen his body and dance aimlessly about on his toes. He has an odd habit of suddenly shaking his head from side to side with extraordinary rapidity and bursting into wild laughter.

PATIENT W. I. (rubella contracted by mother during second month of pregnancy).—This 5½ year old girl shows no understanding of what is dangerous and has to be watched constantly. She is excessively active, destructive and completely unpredictable. She recently threw all the flat silver and whatever else she could lay hands on out of the fourteenth floor window of her home. She frequently becomes wildly hysterical for no apparent reason. Her mother has found that putting her into a tub of cool water will calm her. Now she will climb into the tub herself with all her clothes on and turn on the tap. Sometimes she will turn on the scalding hot water but does not have the perception to get out of the tub or to turn off the water. Toilet training has been unsuccessful. She will urinate while sitting in a chair looking at a book. There is lack of bowel control as well.

PATIENT S. I. (rubella contracted by mother during first month of pregnancy).—This 6 year old boy's favorite activity consists in walking aimlessly about on his toes with his arms upraised writhing above his head, constantly turning and twisting his hands and fingers and yelling at the same time. His stiffened body is flexed forward with his head facing downward. When left to himself, he will do nothing but walk about like this or stretch out on a table, bench or wagon on his back or abdomen and stay in that position for hours at a time. Although he finds chewing solid food not to his liking, he will, when in the country, chew foliage, live grasshoppers, live newly caught fish, etc., with pleasure.

Although each of these three children had his own individual pattern of behavioral peculiarity, all presented certain common problems as well. All were quite oblivious to and disinterested in what was going on about them; it was well nigh impossible to get their gaze or fix their attention for more than brief seconds; all were feeding and toilet problems; all resisted training either violently or with dogged passivity. Further, each had his own peculiar motor mannerism; two employed hand regard even while carrying out other activities. Each had his own particular type of affective outburst—either laughing or crying—without apparent cause. Peculiarities of behavior had been noted since infancy. The traits here mentioned were present when the children first entered school, persisted throughout the entire period of their school attendance and showed little appreciable amelioration at the conclusion of the two year experiment with the special class. At this time, institutional care was recommended and the special class project was discontinued.

INTELLIGENCE AND SCHOOL ACHIEVEMENT

Regular Class Group.—During the course of the first school year, the Merrill-Palmer Scale of Mental Tests[8] was used to determine the respective mental capacities of each member of this group. The children all responded well to the test administration, and intelligence quotients could be obtained for each.[9] The range of intelligence quotients was 73 to 138 with the following distribution: 73, 87, 90, 106, 107, 109, 125, 128, 130, 130, 132, 135 and 138. The mental levels were from "borderline" through "superior."

The mental capacities indicated by these scores were in turn reflected in the quality of class achievement of the respective children. Superior achievement was attained by those whose test results were at superior intelligence quotient levels; satisfactory progress was made by those within the average range, and the two pupils whose test results were below average were unable to advance with the rest of their group. One was eventually placed in a slow-learning class in which she is making adequate progress, and the child with the lowest intelligence quotient had to be dropped from the rolls for lack of ability to master even the preliminary steps of learning after two years. All the other children but one are now mastering speech, lipreading, reading and number work in proportion to their respective mental capacities. In the case of this one other difficulties of an aphasic-like nature appear to be blocking the learning of speech and lipreading, although her achievement in other school subjects is of superior caliber. Such blocking of the learning of speech and lipreading is, however, to be found as well among superior children whose deafness was not caused by maternal rubella and requires special study.

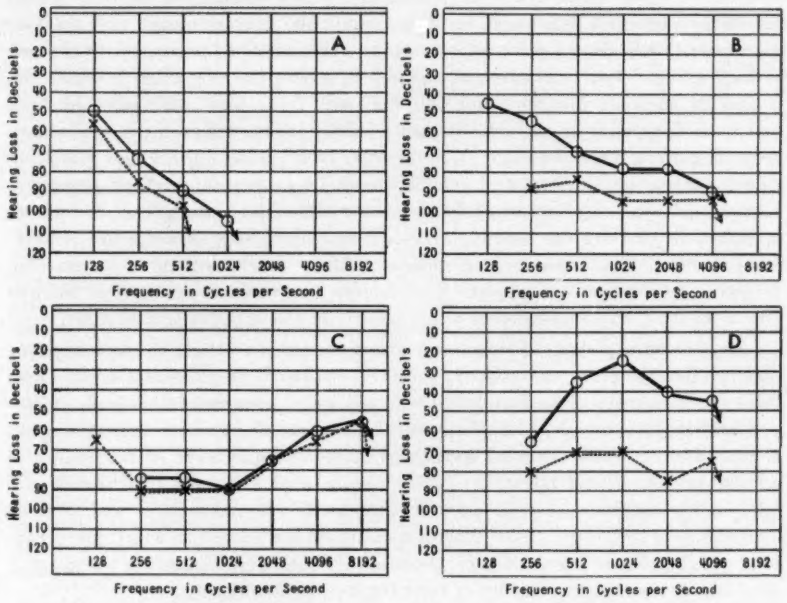
Special Class Group.—The interest and cooperation of these children could be obtained for only a few test tasks of the Merrill-Palmer Scale of Mental Tests. These tasks were generally of the formboard type and were performed rather well. However, intelligence quotients could not be obtained on the basis of these few tasks alone. The respective over-all levels of test performance were of the quality of an approximate mental age of 2½ years. At the time of testing, the chronological ages of the children were 4 years 10 months, 5 years 3 months and 5 years 10 months, respectively. It is difficult to estimate the extent to which the behavioral peculiarities of these children penalized their test performances; but there is no doubt of the defective quality of their functioning intelligence.

As for class achievement, no formal learning or even prelearning activities could be assimilated by these children. As noted above, their goals of learning had been established largely in terms of "humanization," the acquisition of routine procedures and habits and manipulative skills. The type of class activity conducted with them was of the kindergarten variety. At the end of their second year in school, the greatest relative progress was seen in the improvement of their manipulative skills and motor ability. Two of the children became quite adept at putting together formboards and jigsaw puzzles, and all were able to use the outdoor play

8. Stutsman, R.: Mental Measurement of Preschool Children, Yonkers-on-Hudson, N. Y., World Book Company, 1931.

9. Levine, E. S.: Psychological Testing of the Deaf: What Tests; Their Administration and Interpretation in Rehabilitation of Deaf and Hard of Hearing, Selection of Papers Presented at First Institute for Special Workers for Aural Disabled, Washington, D. C., Nov. 28 to Dec. 2, 1949, Staff Development Aids, no. 8, Federal Security Agency, Vocational Rehabilitation Office, Rehabilitation Service Series 117, 1950, p. 15.

equipment more effectively. Some small progress was noted in daily training habits, but this was not consistently maintained. Least progress was made in the areas of socialization and responsiveness to the environment. Side by side with these improvements, however, the children still retained their individual patterns of behavioral peculiarities to about the original degree. It should be mentioned, too, that the improvements that were attained were noted chiefly by those in close daily contact with the children and hardly at all by the casual observer. In the case of one of these children to whom a glutamic acid preparation (glutamicol®)[10] had been administered for over two months, no positive gains whatsoever were achieved and treatment was accordingly discontinued.



A, audiogram typical of nerve deafness, *B*, *C* and *D*, audiograms of children deafened as a result of maternal rubella during pregnancy.

ACOUSTIC PATTERNS

Regular Class Group.—Audiometric tests were successfully administered to 12 of the 13 members of this group by means of the Western Electric 6B Audiometer, air conduction technique. In all cases, hearing loss was found to be binaural, with the range of loss in the better ear from 42 to 104 decibels and in the worse ear from 76 to 110 decibels. The median loss in the better ear of 84 and in the worse ear of 92 decibels is about that expected for deaf children of this age group attending residential schools for the deaf. In nine cases there was a difference of only 6 decibels or less in the amount of hearing loss between the two ears. In three cases there was a greater difference; in one, a difference of 34 decibels; in

10. Levine, E. S.: A Preliminary Report of the Effect of Glutamic Acid Administration upon the Mental Functioning of the Slow Deaf Child, Volta Rev. **51**:269 (June) 1949.

another, of 23 decibels, and in the third, of 15 decibels between the two ears. Eight children of this group are now profitably wearing individual hearing aids.

Of particular interest in the study of the acoustic patterns of these children was the finding that, although the otological diagnosis of nerve deafness had been made in all these cases, the audiogram curves of only three children showed any resemblance to those most usually seen in cases of nerve deafness. The others displayed considerable variation, as the illustrative graphs indicate.

Special Class Group.—None of the three members of this group could be tested audiometrically. However, observation of their respective reactions to various sound situations, both with and without amplification, suggested profound deafness in two children and very mild hearing loss, if any, in one child. This child would occasionally carry out a command spoken behind her back in an ordinary tone of voice. So far as speech was concerned, however, she was mute like her two classmates.

All the children appeared to enjoy sound experiences, although passively, during their acoustic training periods with the group hearing aid. They appeared to enjoy music best. None wore individual hearing aids.

GENERAL HEALTH

Regular Class Group.—With one exception, the general health of the 13 members of this group was good, and their height and weight records showed them to be up to standard in these respects. Except for the one child who was very susceptible to infections of the upper respiratory tract, the attendance records of these children showed few absences because of illness.

The illnesses contracted by these children up to this time have been measles, mumps, chickenpox, whooping cough, pneumonia and otitis media. In all cases diagnoses were made by physicians. Measles was of greatest frequency of occurence, closely followed by chickenpox. Of the 10 children who had had measles, nine had chickenpox as well. Of these nine, five also had mumps and one whooping cough.

None of these children have as yet contracted rubella.

Special Class Group.—All three of these children measured up to height and weight standards, although two were on the thin side, and the general health of two was good. The third child was absent because of illness in about the same proportion of the time as he was present in school. He suffered mainly from infections of the upper respiratory tract and occasional periods of digestive disorder. The attendance records of the other two showed infrequent absence because of illness.

The illnesses contracted by these children up to the present have been intestinal influenza and occasional colds in one child; otitis media, chickenpox and more frequent but mild colds in another, and tonsillitis, measles and very frequent infections of the upper respiratory tract in the third child.

None of these children have as yet contracted rubella.

COMMENT

Of the 16 children with whom this study deals, all born deaf following maternal rubella during pregnancy, 12 are still in attendance at schools for the deaf, where they are making satisfactory to excellent progress. No peculiarities of behavior or

other developmental anomalies have made an appearance up to this time. From the educator's viewpoint these children are normal, educable deaf pupils.

Of the four remaining members of the orginal group, one was removed from the Lexington School by his parents because he was unable to make adequate school progress. This child was of borderline intelligence. He was enrolled at another school for the deaf but has thus far been unable to make satisfactory progress there as well.

The special class project, devised for the three most seriously affected children, was discontinued at the end of the second year for lack of any appreciable progress on the part of these children. Institutional care was recommended; but thus far only one parent has taken steps in this direction. The others resented the suggestion bitterly and succeeded in having their children admitted to other schools for the deaf. They have since been dismissed from these schools. From the educator's viewpoint they are uneducable.

SUMMARY

The relation between rubella infection during early pregnancy and various congenital defects in the infant—notably acoustic defects—has been confirmed by reports from various workers throughout the world.

It was considered timely to investigate the psychoeducational patterns of children born deaf following maternal rubella during pregnancy. The present summary is accordingly based on a study of the behavior, intelligence, school achievement, acoustic patterns and general health of a group of 16 such children in their first two years of school life. Their ages at the time of school admission ranged from 3 years to 4 years 10 months.

In all cases rubella had been contracted by the mother within the first three months of pregnancy. Other physical defects present among the children were ocular defects, systolic murmur, cervical adenitis, umbilical hernia, pigeon breast, enlarged spleen, aphagia, digestive disorder and cryptorchism.

In regard to behavior, 13 of the 16 children behaved much the same as their deaf peers, except for their greater tendency to hyperactivity, tenseness and low stimulus threshold. In the other three children, however, the behavior was strongly suggestive of brain damage or disease, combining infantile characteristics, defective mentality, inappropriate responsiveness and queer motor mannerisms. Unfortunately, these children resisted neurological study.

Intelligence testing of the 13 children to whom such tests could be successfully administered disclosed a range of borderline through superior, with only one child in the former category and seven in the latter. The expected school progress was made by these children in accordance with their respective mental capacities. The three seriously affected children could not be tested successfully. Their functioning intelligence was defective.

The results of audiometric testing revealed the presence of binaural hearing loss throughout the frequency range, with the expected amount of loss for this age group. The type of acoustic defect was diagnosed as nerve deafness, but in only three cases did the audiograms approximate the curves most usually associated with such deafness. Eight of the children are able to derive great benefit from individual hearing aids. In the three seriously affected children audiometric testing could not be carried out, but observation suggested that two were profoundly deaf and that one had very little hearing loss, if any.

All children were up to standard in height and weight, although only a few were robust. General health was good. The illnesses contracted by the children thus far have been measles, mumps, chickenpox, whooping cough, pneumonia, otitis media, tonsillitis and colds. Measles and chickenpox were by far of greatest frequency of occurrence. None of the children have as yet contracted rubella.

To conclude, from the evidence of this study it appears that deaf children with a maternal history of rubella during pregnancy fall into two main classes, educationally considered: (1) those who are educable and in whom the major developmental handicap is deafness and (2) those who are uneducable and in whom the developmental handicaps are deafness, mental defect and behavioral peculiarities suggestive of brain damage. The evidence further indicates that developmental peculiarities make themselves apparent as far back as early infancy. In such cases it is wise to prepare the parents for the possibility of institutionalization of the child. The mental anguish and emotional turmoil these parents are destined to suffer unless adequately prepared warrant particular consideration.

For the same reason, the association between congenital defects and maternal rubella during pregnancy should be given wide publicity in order that parents and children both may be protected against this relatively mild illness which may, nevertheless, have such serious consequences. Suggestions concerning possible means of protection are presented by Patrick.[11]

11. Patrick, P. R.: Report of a Survey of Children Born in 1941 with Reference to Congenital Abnormalities Arising from Maternal Rubella, M. J. Australia **1**:421, 1948.

TREATMENT OF TYPHOID IN CHILDREN WITH CHLORAMPHENICOL (CHLOROMYCETIN®)

Report of Seven Cases

JOSEPH GREENGARD, M.D.
LAWRENCE BRESLOW, M.D.
AND
ALBERT MILZER, Ph.D., M.D.
CHICAGO

IN THE year 1948 Woodward [1] obtained excellent results in the treatment of 10 patients with endemic typhoid on the Malay Peninsula with chloramphenicol (chloromycetin®). Two patients relapsed, but a second course of therapy was effective. By 1949 this series had been extended to 44 cases, with continued excellent results.[2] Further reports on the treatment of endemic typhoid with chloramphenicol in India have been made by Shah,[3] Vakil [4] and Patel.[5] In the 53 cases reported by them, there were 7 relapses which responded to a second course of therapy and 3 deaths [5] occurring in the first 48 hours of treatment. Shah [3] felt that results were excellent only in those cases in which treatment was started before the tenth day of illness. Knight [6] treated 13 patients in Mexico, with good results. Murgatroyd [7] reported one case from Great Britain in which treatment for only seven days resulted in an uneventful recovery. Bradley [8] reported the treatment of

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Some of the chloramphenicol used was supplied by Parke, Davis & Company, Detroit, through Dr. B. M. Kagan, Director of Pediatric Research, Michael Reese Hospital.

Miss Naomi McElwaine gave technical assistance.

1. Woodward, T. E.; Smadel, J. E.; Ley, H. L.; Green, R., and Mankinar, D. S.: Preliminary Report on the Beneficial Effect of Chloromycetin in the Treatment of Typhoid Fever, Ann. Int. Med. **29**:131 (July) 1948.

2. Smadel, J. E.; Woodward, T. E., and Bailey, C. A.: Relation of Relapses in Typhoid to the Duration of Chloramphenicol Therapy, J. A. M. A. **141**(pt. 2):129 (Sept. 10) 1949.

3. Shah, M. J.: Chloromycetin in Typhoid Fever, Indian Physician **7**:192 (July) 1949.

4. Vakil, R. J.: Chloromycetin in Enteric Fever, Indian Physician **7**:185 (July) 1949.

5. Patel, J. C.; Banker, D. D., and Modi, C. J.: Chloramphenicol in Typhoid Fever, Brit. M. J. **2**:908-909 (Oct. 22) 1949.

6. Knight, V.; McDermott, W., and Ruiz-Sandrez, F.: Aureomycin and Chloramphenicol: Use in Typhus, Typhoid and Brucellosis, J. Clin. Invest. **28**:1052, 1949.

7. Murgatroyd, F.: Typhoid Treated with Chloromycetin, Brit. M. J. **1**:851 (May 14) 1949.

8. Bradley, W. H.: Chloromycetin in Typhoid Fever, Lancet **1**:869 (May 21) 1949.

10 patients during an epidemic in England resulting from a contaminated beverage. Nine patients made a complete recovery; the tenth died after 24 hours of therapy. Lomax [9] reported one case in which results were excellent. In general, most of these authors followed Woodward's [1] therapeutic schedule: 0.050 Gm. per kilogram of body weight as the initial dose, 0.25 Gm. every two hours until defervescence occurs and then 0.25 Gm. every four hours for five days.

Foster [10] reported the case of a college student who aspirated an attenuated culture of Salmonella typhosa and became ill with the typical symptoms in 11 days. After three days of streptomycin therapy had failed to bring about any improvement, chloramphenicol was given, 3.0 Gm. a day, with defervescence occurring by the third day. Stiller [11] was the first to report the use of chloramphenicol for typhoid in a child. The patient, a 6 year old girl, was in the nineteenth day of her illness and was doing poorly when administration of chloramphenicol, 0.075 Gm. per kilogram a day, was started. Her temperature dropped in 16 hours, and she made an uneventful recovery.

These reports were all encouraging, and since detailed study of chloramphenicol had failed to reveal any serious toxic effects,[12] we treated our first patient in April 1949. In the remainder of 1949 six other patients were seen and treated at this hospital. In view of the few reports on the use of this drug in therapy of typhoid in children, we felt that our observations would be significant.

REPORT OF CASES

CASE 1.—J. L., a 4 year old Negro girl, was admitted on April 29 because of vomiting and paraumbilical pain of 18 days' duration and headache, fever and lethargy of seven days' duration. The family history elicited no recent illness in the parents or in six siblings. Examination revealed an acutely ill, dehydrated child with rectal temperature of 104 F., pulse rate of 140 and respiration rate of 24 a minute. There were a mucopurulent nasal discharge and distention of the abdomen but no other significant physical findings.

Urinalysis revealed the presence of acetone, albumin, an occasional leukocyte and a few granular casts. The erythrocyte sedimentation was 24 mm. an hour. Serum agglutination reactions were negative for S. typhosa, other Salmonella, Brucella, the Weil-Felix test, Bacterium tularense and the heterophil antigens. Cold agglutinins were absent. Serologic studies for the various viruses and rickettsias also gave negative reactions. Other pertinent laboratory data are shown in chart 1.

The passage of several small foul, liquid stools shortly after admission led to a tentative diagnosis of acute enterocolitis. Initial therapy consisted in administration of sulfadiazine and streptomycin orally with fluids parenterally to combat the dehydration. Despite these measures the abdominal distention increased, the diarrhea persisted and the liver and spleen were both palpable and tender.

On May 4 since the admission blood culture revealed S. typhosa, the patient was given chloramphenicol exclusively, 1.5 Gm. a day in divided doses (0.075 Gm. per kilogram). Sensitivity tests showed inhibition by streptomycin, 20 micrograms per cubic centimeter;

9. Lomax, W.: Chloramphenicol in Typhoid Fever, Brit. M. J. **2**:911-912 (Oct. 22) 1949.

10. Foster, W. D., and Condon, R. J.: The Treatment of Acute Typhoid Fever with Chloromycetin,® J. A. M. A. **141**:131 (Sept. 10) 1949.

11. Stiller, R.: Typhoid Fever Treated with Chloromycetin, J. Pediat. **35**:85 (July) 1949.

12. (*a*) Hess, J. H., and Lundeen, E. C.: The Premature Infant: Medical and Nursing Care, ed. 2, Philadelphia, J. B. Lippincott Company, 1949, p. 180. (*b*) Schoenbach, E. B.: Edward Gamaliel Janeway Lecture; The Newer Antibiotics: Polymyxin, Chloromycetin and Aureomycin, J. Mt. Sinai Hosp. **16**:71 (July-Aug.) 1949. (*c*) Ley, H. L., Jr.; Smadel, J. E., and Crocker, T. A.: Administration of Chloromycetin to Normal Human Subjects, Proc. Soc. Exper. Biol. & Med. **68**:9 (May) 1948. Woodward, Smadel and Ley.[1]

aureomycin, 4 micrograms, and chloramphenicol, 3 micrograms. Marked improvement was noted on the third day. The child made an uneventful convalescence, administration of chloramphenicol being discontinued on May 19, the fifteenth day of therapy, after 22.5 Gm.

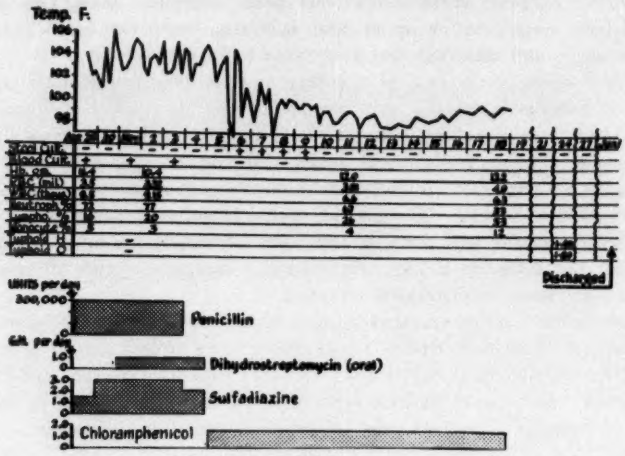

Chart 1 (case 1).—J. L., a 4 year old Negro girl, was treated ineffectively with penicillin, dihydrostreptomycin given orally and sulfadiazine but responded rapidly to treatment with chloramphenicol, 0.075 Gm. per kilogram (total dose, 22.5 Gm.).

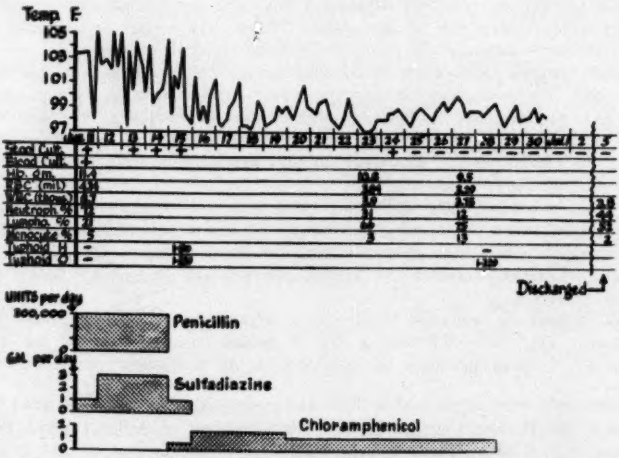

Chart 2 (case 2).—P. M., a 3 year old Negro girl, was treated with chloramphenicol beginning the twelfth day of illness in doses of 0.1 Gm. per kilogram (total dose, 15.5 Gm.).

had been taken. No ill effects were noted from the drug. Blood cultures were negative for S. typhosa after the third day of therapy (twenty-sixth day of illness); stool cultures, after the fifth day of therapy. Detailed blood counts and the results of serum agglutination tests are shown in chart 1.

CASE 2.—P. M., a 3 year old Negro girl, was admitted on June 11 because of cough, abdominal pain and fever of seven days' duration. The administration of sulfadiazine and penicillin had not brought about any improvement in the child's condition, and shortly before being brought to the hospital she had passed several foul, watery, mucoid stools. The family history was noncontributory. On examination the child appeared acutely ill, toxic and dehydrated, with a rectal temperature of 103.2 F. The pharynx was injected, and there were a few rales heard over the left side of the chest, posteriorly. Urinalysis revealed the presence of acetone, albumin, a few erythrocytes, leukocytes and hyaline casts. The erythrocyte sedimentation rate was 26 mm. an hour. Serum agglutination tests gave negative reactions.

On June 15 S. typhosa was isolated from cultures of stools and blood obtained on admission. Serum agglutination reactions were positive for typhoid H antigen in a 1:80 dilution and for typhoid O antigen in a 1:320 dilution. Sensitivity tests by the turbidity method[12a] showed complete inhibition by streptomycin, 20 micrograms per cubic centimeter, and chloramphenicol, 2 micrograms per cubic centimeter. In therapeutic amounts sulfadiazine showed complete and sulfathiazole partial inhibition of growth in vitro.[13]

On June 15, the twelfth day of illness, the child was given chloramphenicol exclusively, 0.25 Gm. every four hours (0.1 Gm. per kilogram of body weight). There was marked improvement in 24 hours. On June 20 the dosage was reduced to 0.25 Gm. every six hours, and on June 28, after 13 days of therapy, use of the drug was discontinued, a total of 15.5 Gm. having been taken. There was some nausea, but no emesis occurred. The sharp drop in leukocyte count, which occurred during therapy, as well as results of additional stool cultures and agglutination tests, are shown in chart 2. Convalescence was uneventful.

CASE 3.—J. M., a 4 year old Negro boy, was admitted on July 25 because of fever, listlessness, paraumbilical pain and intermittent diarrhea of six days' duration. The past history and family history were essentially noncontributory. Examination revealed an acutely ill, listless child with a rectal temperature of 103.6 F., an injected pharynx and marked distention of the abdomen. The liver and spleen were not palpable. Urinalysis revealed albumin, leukocytes, erythrocytes and a few granular casts. The erythrocyte sedimentation rate was 24 mm. an hour. Serum agglutination reactions were negative for typhoid H antigen but positive in a dilution of 1:320 for the O antigen.

On July 27 stool and blood specimens obtained on admission were found to be positive for S. typhosa. The following are the results of sensitivity tests: inhibition of growth by streptomycin, 5 micrograms per cubic centimeter and chloramphenicol, 4 micrograms per cubic centimeter, and partial inhibition of growth by therapeutic amounts of sulfathiazole and sulfadiazine. Administration of chloramphenicol orally, 0.25 Gm. every four hours (0.08 Gm. per kilogram a day), was begun. Although there was a temporary period of improvement, clinical and roentgen evidence of a bilateral bronchopneumonia soon developed. Penicillin, oxygen and blood transfusions were used to combat this complication, and by July 30 the child appeared much improved. At this time a relapse occurred which was attributed to dehydration and possibly to myocarditis. However, on August 2 the temperature dropped suddenly and remained normal during the rest of the hospital stay. Use of penicillin was discontinued on August 5, and chloramphenicol administration, having been reduced to 0.25 Gm. every six hours on August 3, was discontinued on August 8, the thirteenth day of therapy, a total of 15.5 Gm. having been given. There was no untoward reaction to the drug except for nausea and vomiting. Pseudomonas aeruginosa persisted in many of the stools examined during and after therapy. Data on blood counts, cultures and agglutination tests are summarized in chart 3.

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13. The following unpublished screening test is used at Michael Reese Hospital to determine in vitro sensitivity to sulfadiazine and sulfathiazole: Nutrient or blood agar plates are prepared containing a final concentration of 100 mg. per 100 cc. of the soluble salt of the test sulfonamide. The sulfonamide plates together with a control plate are seeded with 0.05 cc. of 1:1,000 and 1:10,000 dilutions of a six hour broth culture of the test organism. The plates are incubated at 37 C. for 24 hours, and the degree of inhibition is noted by comparing the amounts of growth on the sulfonamide and on the control plates. In general we have found that there is some correlation between complete inhibition of growth by a given sulfonamide and therapeutic effect. On the other hand, even partial inhibition of growth by a sulfonamide in this test is sometimes correlated with a therapeutic response.

CASE 4.—R. M., the sister of J. M., a 6 year old Negro girl, was admitted on August 15 because of intermittent fever, abdominal pain, persistent headache and occasional green, foul, watery stools of two weeks' duration. Examination revealed a toxic, dehydrated, seriously ill child with a rectal temperature of 102.4 F., a moderately distended abdomen and a liver palpable 2 cm. below the costal margin. Urinalysis showed the presence of albumin, acetone and an

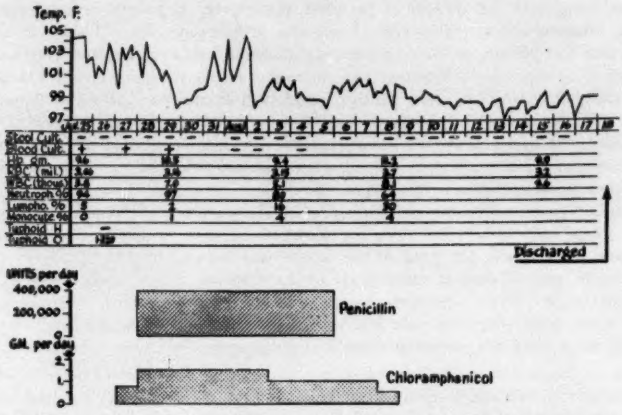

Chart 3 (case 3).—J. M., a 4 year old Negro boy, was treated with chloramphenicol in doses of 0.08 Gm. per kilogram and simultaneously with penicillin because of a complicating bronchopneumonia (total dose of chloramphenicol, 15.5 Gm.).

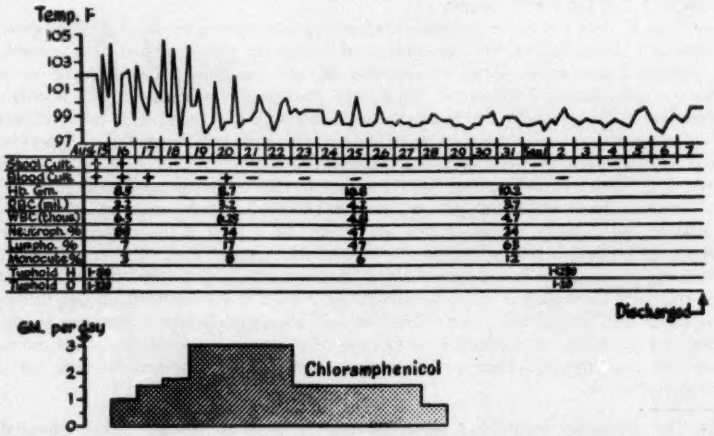

Chart 4 (case 4).—R. M., 6 year old sister of J. M., was treated with chloramphenicol beginning the nineteenth day of illness in doses of 0.071 Gm. per kilogram, later in doses of 0.142 Gm. per kilogram because of lack of appreciable effects (total dose, 22.5 Gm.).

occasional erythrocyte, leukocyte and hyaline cast. The erythrocyte sedimentation rate was 21 mm. an hour. Both the stool and the blood cultures were positive for S. typhosa, the Widal test showing agglutination with the H antigen in a dilution of 1:80 and with the O antigen in a dilution of 1:320 (chart 4).

Sensitivity tests showed complete inhibition by 10 micrograms of streptomycin per cubic centimeter, 4 micrograms of chloramphenicol, 8 micrograms of aureomycin and sulfathiazole in therapeutic amounts. On August 16, the nineteenth day of illness, administration of chloramphenicol orally was started, 0.25 Gm. every four hours (0.071 Gm. per kilogram a day). On August 19, there having been little improvement in the child's condition, the chloramphenicol dose was increased to 0.5 Gm. every four hours (0.142 Gm. per kilogram a day). The temperature dropped appreciably on that day and continued to fall by lysis until August 22, after which it remained normal.

Stool cultures became negative for S. typhosa on August 18, the third day of therapy. The blood cultures remained positive for S. typhosa until August 21, the sixth day of therapy (chart 4). On August 22 the dose was reduced to 0.25 Gm. every four hours, and on August 28 administration of chloramphenicol was discontinued, a total of 22.5 Gm. having been given in 12 days. A rather sharp drop in leukocyte count occurred during therapy (chart 4). The child left the hospital on September 7 still showing a moderate hypochromic anemia and persistent hepatomegaly.

CASE 5.—L. P., a 6 year old Negro boy, was admitted on September 4 with a history of chills, fever and headache of four days' duration. Family history and past history were noncontributory. Examination revealed an apparently well child with 100.6 F. rectal temperature, and a soft systolic murmur over the apex, but there were no other significant physical findings.

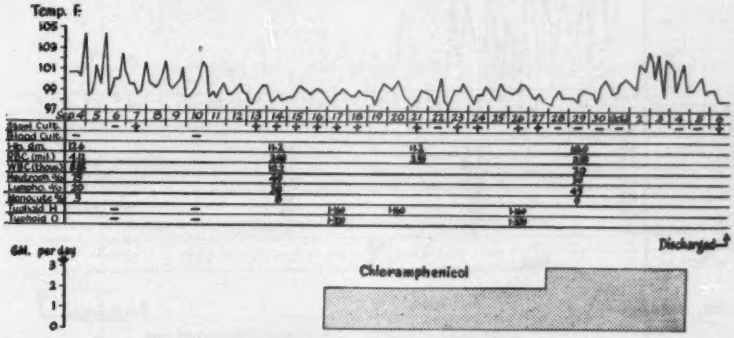

Chart 5 (case 5).—L. P., a 6 year old Negro boy, was not ill when therapy was initiated, but stools yielded S. typhosa. This was considered a clinical case of typhoid rather than a carrier case because of the development of typhoid H and O antibodies while the patient was under observation. The dose of 0.095 Gm. per kilogram was later increased to 0.136 Gm. (total dose, 34 Gm.).

Urinalysis revealed the presence of acetone, a trace of albumin and an occasional erythrocyte and leukocyte. The erythrocyte sedimentation rate was 23 mm. an hour. Roentgen examination of the chest showed nothing abnormal. Serum agglutination tests gave negative results; blood and stool cultures did not yield pathogens.

The child appeared quite well except for an evening rise in temperature and a moderate hepatomegaly. A stool examined on September 10 was positive for S. typhosa; but the results of serum agglutination tests were negative, and blood cultures remained sterile. Sensitivity tests showed complete inhibition by sulfadiazine and sulfathiazole; chloramphenicol, 4 micrograms per cubic centimeter; aureomycin, 6 micrograms per cubic centimeter, and streptomycin, 20 micrograms per cubic centimeter. Although the patient's temperature remained normal after September 11, without specific therapy, serum agglutination reactions on September 17 were positive for typhoid H and O antigens in titers of 1:160 and 1:320 respectively. Since stool cultures still yielded pathogens, chloramphenicol administration was started, 0.25 Gm. every three hours (0.095 Gm. per kilogram a day). On September 28 the dose was increased to 0.5 Gm. every four hours (0.136 Gm. per kilogram a day), and the stool cultures, which had remained positive for S. typhosa, immediately became negative. Therapy was discontinued on October 4, after 18 days, 34 Gm. having been given. There had been no untoward reactions to this antibiotic. Blood counts remained normal (chart 5).

On October 2 a pharyngitis associated with fever developed. The child was discharged on October 6. A stool obtained on the day of the patient's discharge from the hospital subsequently showed the presence of S. typhosa. However, follow-up stool cultures yielded no pathogens, and the child has remained asymptomatic.

Case 6.—L. M., a 4 year old Negro girl, was admitted on September 18 with a history of recurrent bouts of high fever, intermittent abdominal pain, listlessness and transient swelling of both the eyelids and feet, of four days' duration. She had received sulfadiazine orally and penicillin parenterally for several days at home, without improvement. The past history revealed that the patient had been exposed to pneumonia two weeks prior to her illness. On examination an acutely ill, apathetic, toxic child was seen, with a rectal temperature of 104.6 F., a moderately injected pharynx and a postnasal mucoid discharge. Urinalysis showed the presence of albumin, with an occasional erythrocyte and leukocyte in the sediment. The erythrocyte sedimentation rate was 31 mm. an hour. Serum agglutination tests gave negative results.

On September 24, the tenth day of illness, a stool culture was found to be positive for S. typhosa, and repeated serum agglutination tests showed a positive reaction with the O antigen

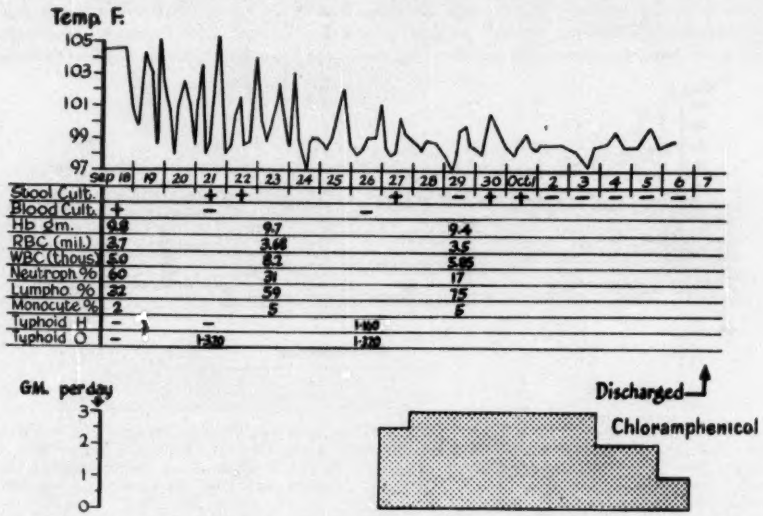

Chart 6 (case 6).—L. M., a 4 year old Negro girl, was treated with 0.187 Gm. chloramphenicol per kilogram a day. Total neutrophil count dropped from 3,000 per cubic millimeter to 994 per cubic millimeter but returned spontaneously to normal.

in a dilution greater than 1:320. Two days later a culture of blood drawn on admission was positive for S. typhosa, and serum agglutination reactions were positive for the H antigen in a dilution greater than 1:160. Sensitivity studies showed complete inhibition of growth by sulfathiazole and sulfadiazine, by 40 micrograms per cubic centimeter of streptomycin and by 4 micrograms per cubic centimeter of chloramphenicol.

Although the child's condition continued to improve, the stool cultures remained positive for S. typhosa. On September 27 administration of chloramphenicol was begun, 0.5 Gm. every four hours (0.187 Gm. per kilogram a day). Stool cultures positive for S. typhosa appeared intermittently until October 3 (the sixth day of therapy and nineteenth day of illness), after which all were negative. On October 4 the dose was reduced to 0.5 Gm. every six hours, and administration of the drug was discontinued on October 6, stool cultures having been negative for pathogens for three days. The child was discharged from the hospital on October 6, the blood, which had shown a drop in leukocytes during therapy, having returned to normal (chart 6). A follow-up stool culture on October 30 was negative for S. typhosa.

CASE 7.—S. B., a 6 year old Negro girl, was admitted on December 2 with a history of paraumbilical pain and fever for five days. There had been one liquid stool on the day of admission. The past history and family history were irrelevant. Examination revealed an acutely ill, toxic, dehydrated child with a rectal temperature of 104.6 F., injection of the pharynx and a few coarse rales at the base of both lungs. The abdomen was soft and non-tender. The liver and spleen were not enlarged. While being examined the child passed a pea green watery stool.

Laboratory examination revealed the presence of albumin, a few casts and an occasional erythrocyte and leukocyte in the urine. The erythrocyte sedimentation rate was 37 mm. in one hour. Serum agglutination tests gave completely negative reactions, except for typhoid H antigen, which gave a positive reaction in a dilution of 1 : 80. A stool culture was negative for S. typhosa, but a culture of blood drawn on admission was reported positive on December 6. Stool cultures later became positive for S. typhosa (chart 7). At this time, the liver was palpable 3 cm. below the costal margin and the spleen was barely palpable. Since in vitro sensitivity tests showed complete inhibition by 2 micrograms of chloramphenicol per cubic centimeter, therapy was started on December 6. (There was also complete inhibition by

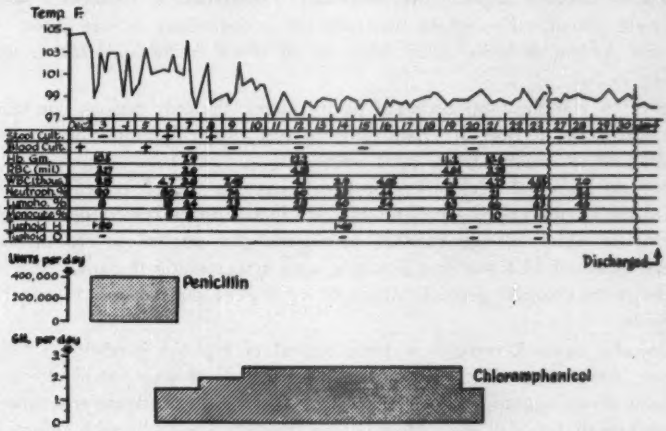

Chart 7 (case 7).—S. B., a 6 year old Negro girl, was treated with chloramphenicol, initially with 0.075 Gm. per kilogram and after 48 hours with 0.125 Gm. per kilogram. The child demonstrated a drop in red cell count and hemoglobin level to 3,000,000 and 7.9 Gm. on the second day of therapy and a drop in leukocyte count to 4,300, with 16 per cent neutrophils on the fourteenth day of therapy.

sulfathiazole, sulfadiazine and 20 micrograms per cubic centimeter of streptomycin but resistance to 8 micrograms of aureomycin.)

The initial dose of chloramphenicol was 0.5 Gm. every four hours for three doses; then 0.25 Gm. every four hours (0.075 Gm. per kilogram of body weight each 24 hours) was given. This amount was increased on December 8 to 2.0 Gm. a day and on December 10 to 2.5 Gm. a day (0.125 Gm. per kilogram a day). The child was alert, hungry and much improved in 24 hours, although there was no dramatic change in the temperature curve until the fifth day of therapy. A culture of blood drawn 24 hours after the start of therapy, the tenth day of illness, was sterile. The stools were negative for S. typhosa after the third day of treatment (chart 7).

On December 7, the second day of therapy, the hemoglobin level had dropped to 7.9 Gm., with 3,000,000 erythrocytes. On December 10 a 400 cc. transfusion of compatible blood was given. On December 19, the fourteenth day of therapy, the leukocyte count had fallen to 4,300, with 16 per cent neutrophils, 63 per cent lymphocytes, 16 per cent monocytes, 2 per cent eosinophils, 1 per cent basophils and 2 per cent plasma cells. Bone marrow study showed a full

marrow with a slight shift to the left in the myelocytic series, an increase in eosinophils and monocytes but no evidence of maturation arrest.

Use of chloramphenicol was discontinued on December 20, the fifteenth day of therapy, 33.5 Gm. of the drug having been given. The leukocyte count remained about 4,400, with 20 per cent neutrophils, until eight days after therapy was discontinued, when it rose to 7,000, with 34 per cent neutrophils (chart 7). Although further stool cultures were negative for S. typhosa, Proteus morganii was isolated repeatedly. The child was discharged on January 4 and has remained well to the present time.

COMMENT

The diagnosis of typhoid in children is dependent on awareness of the atypical symptoms that may accompany the disease. Halpern [14] regards the presence of headache, fever and abdominal pain as the three commonest symptoms of typhoid in children. Diarrhea occurred in only 37 per cent of his series, rose spots in 39 per cent and a palpable spleen in only 50 per cent.

In our seven cases diagnosis was confirmed by blood and stool cultures in addition to positive agglutination reactions. Bradycardia, leukopenia and rose spots were absent. The spleen was palpable in only three of our cases. Headache was present in three cases, fever in all seven, abdominal pain in six and diarrhea in five.

Very few complications occurred in our series, the only serious one being the pneumonia seen in case 3. Although we feel that chloramphenicol may have prevented these complications, it is interesting to note that Halpern,[14] in 1929, reported no intestinal perforation or hemorrhage in the 67 patients he studied. Most of the complications seen by him were in the upper respiratory system. In addition, he observed one case of meningitis and one of severe myocarditis. Halpern reported 13.4 per cent fatalities with symptomatic therapy. We had no fatalities with chloramphenicol, although we regard our series too small to be conclusive.

Clinically cases 1 through 4 were typical of typhoid in children. Case 5, however, was not at all characteristic, and the patient was considered a carrier before the serum agglutination titers for typhoid H and O antigens rose sharply, on the seventeenth day of illness. He was then treated successfully with chloramphenicol for 18 days. The temporary recurrence of a stool positive for S. typhosa, as seen in this case, is not unusual according to Woodward,[1] and follow-up stool cultures were negative. Also, in case 6 the patient made a clinical recovery before the institution of specific therapy, although stool cultures continued to show S. typhosa. In neither of these two cases could we feel that chloramphenicol had played an important role, but in the other five cases there was no question about the prompt and dramatic clinical response to the drug.

The amount of chloramphenicol used at the start of therapy varied from 0.071 to 0.187 Gm. per kilogram per 24 hours. In most cases the original dose seemed high enough to produce a satisfactory clinical response, and as soon as this response was seen, the quantity was reduced. In three cases the original dose of the drug was increased—in cases 4 and 7 the increase occurred in the first few days of therapy because of the continuance of fever; in case 5 the increase occurred on the eleventh day of therapy because stool cultures continued to show S. typhosa. These observations led us to believe that an original dose of 0.100 Gm. per kilogram a day

14. Halpern, L. J.: Typhoid Fever in Children, Am. J. Dis. Child. **38**:10-15 (July) 1929.

is necessary in children. Ross,[15] however, in treating Salmonella infections other than typhoid in infants used 0.110 to 0.480 Gm. per kilogram a day, administered in aromatic eriodictyon syrup (syrup of yerba santa), and felt that this dose of chloramphenicol was necessary to produce a clinical response.

The bacteriologic follow-up on these cases was extremely interesting, especially the persistence of S. typhosa in blood cultures after the start of therapy (table 1). In the two cases caused by S. typhosa phage type F_2 (cases 3 and 4) we found blood cultures to yield pathogens on the second and fourth day of therapy. Although both children had shown some drop in temperature, there was little clinical evidence of decrease in toxicity until the blood cultures became sterile. It was necessary to double the dose of chloramphenicol for one child (case 4) before improvement occurred clinically or bacteriologically.

Woodward [1] originally reported that blood cultures taken after chloramphenicol administration was started, even as early as two hours after the first treatment, were all sterile. In a subsequent report,[16] however, he stated that blood cultures had

TABLE 1.—*Summary of Bacteriologic Studies and Response to Therapy*

Case	Phage Type	Duration of Disease Prior to Therapy, Days	Duration of Therapy, Days	Original Dose Chloramphenicol, Gm./Kg./Day	Total Chloramphenicol Taken, Gm.	Duration of Therapy (Days) Prior to: Stool Culture Negative for S. Typhosa	Duration of Therapy (Days) Prior to: Blood Culture Negative for S. Typhosa	Duration of Therapy (Days) Prior to: Normal Temperatures
1	...	25	15	0.075	22.5	6	1	3
2	B_1	12	13	0.1	15.5	9	*	2
3	F_2	8	13	0.08	15.5	†	3	2 to 8 ‡
4	F_2	19	12	0.071 to 0.142	22.5	2	5	5
5	J	17	18	0.095 to 0.136	34.0	12	†	§
6	J	13	9	0.187	25.0	6	‖	‖
7	J	9	15	0.075 to 0.125	33.5	7	1	4

* Culture not repeated.
† Never positive for S. typhosa.
‡ Typhoid complicated by pneumonia.
§ Normal without therapy.
‖ Sterile without therapy.

been positive for S. typhosa after 24 hours for two patients and after 48 hours for two others. Collins [17] reported a blood culture positive for S. typhosa 48 hours after the start of therapy in one case and in another, 72 hours after readministration of the drug to a patient who had relapsed despite 13 days of therapy. The persistence of pathogens in blood cultures does not seem to be related to the duration of the disease prior to the start of therapy or to the amount of the drug used in treatment. However, these findings are in general agreement with those of most authors [18] that the temperature of the average patient treated with chloramphenicol

15. Ross, S.; Burke, F. G.; Rice, E. C.; Washington, J. A., and Stevens, S.: Chloromycetin in the Treatment of Salmonella Enteritis, New England J. Med. **242**:173 (Feb. 2) 1950.

16. Woodward, T. E.; Smadel, J. E., and Ley, H. L.: Chloramphenicol and Other Antibiotics in the Treatment of Typhoid Fever and Typhoid Carriers, J. Clin. Invest. **29**:87 (Jan.) 1950. 1950.

17. Collins, H. S., and Finland, M.: Treatment of Typhoid Fever with Chloromycetin, New England J. Med. **241**:556 (Oct. 13) 1949.

18. (*a*) Erickson, G. W.: Treatment of Typhoid Fever with Chloromycetin, New England J. Med. **242**:177 (Feb. 2) 1950. (*b*) Briggs, J. N.: Relapse in Typhoid Fever After Treatment with Chloramphenicol, Lancet **1**:115 (Jan. 21) 1950. Footnotes 1 to 11, 16 and 17.

does not return to normal until several days of therapy have elapsed. Woodward [16] found the average duration of fever to be 3.5 days, which coincides with our observations. We also confirmed Woodward's observation that despite the persistence of fever most patients showed marked clinical improvement within 12 to 24 hours after the start of therapy.

There was only one child (case 5) who showed a return of the organism in his stool after therapy was discontinued. However, further therapy was not given, and the stools became free of S. typhosa in several weeks. Woodward [1] also found the spontaneous return to stools free of S. typhosa in two of his patients who had appeared on the verge of becoming carriers.

In addition to the S. typhosa isolated in the stools of all but one patient (case 3), we also found Endameba histolytica (case 1), Ps. aeruginosa (case 3) and P. morganii (case 7). None of these other organisms were influenced by chloramphenicol therapy.

During the eight month period covered by this report (April 29 to Dec. 15, 1949) there were 15 children treated for typhoid in this and other Chicago hospitals. These patients were all Negro children who came from the same over-

TABLE 2.—*In Vitro Sensitivity Studies on S. Typhosa**

Case	Chloramphenicol, Mcgm./Cc.	Streptomycin, Mcgm./Cc.	Aureomycin, Mcgm./Cc.	Sulfathiazole	Sulfadiazine
1	8	20	4	..	..
2	2	20	..	±	+
3	4	5	..	±	±
4	4	10	8	+	..
5	4	20	6	+	+
6	4	40	..	+	+
7	2	20	8	+	+

* Complete inhibition by therapeutic amounts is indicated by +; partial inhibition by therapeutic amounts, by ±.

crowded slum area. Of the seven patients reported here, three (cases 1, 3 and 4) had been playing in flooded basements and one (case 2) had been in contact with a carrier and in three (cases 5, 6 and 7) the infection was unexplained. However, it was found that the latter three had all been eating "snowballs," a shaved ice and syrup concoction sold by street vendors, and it is believed that this may have been the source of infection. Bacteriophage typing [19] revealed three types: type F_2 in cases 3 and 4, type B in case 2 and type J in cases 5, 6 and 7. It can be seen that these results tend to confirm the epidemiological grouping described above. It was also found that in cases 1, 3 and 4, apparently resulting from flooded basements, the patients were much more seriously ill than any of the other patients in this series.

In vitro sensitivity tests were carried out with use of the organisms recovered from all seven patients (table 2). Smith [20] reported inhibition of S. typhosa by 0.25 micrograms of chloramphenicol per cubic centimeter, the lowest concentration of any antibiotic studied. He found inhibition in vitro by other antibiotics such as

19. Miss F. Friewer of the Illinois Department of Public Health performed the bacteriophage typing.

20. Smith, R. M.; Joslyn, D. A.; Gruhzit, O. M.; McLean, I. W., Jr.; Penner, M. A., and Ehrlich, J.: Chloromycetin: Biological Studies, J. Bact. **55**:425 (March) 1948.

penicillin and streptomycin, but only in much greater concentrations. Collins [17] found it necessary to use 4 to 8 micrograms of chloramphenicol per cubic centimeter in order to inhibit growth of the typhoid strains isolated from his patients. For four of our seven cases 4 micrograms of chloramphenicol were needed to produce inhibition of the organism, and we also noted complete inhibition with relatively small concentrations of streptomycin, aureomycin and the sulfonamides. However, except for chloramphenicol, none of these drugs was effective in treatment of the patient. For example, in case 2 there was complete inhibition of growth of the S. typhosa recovered from the stool by therapeutic concentrations of sulfadiazine, but after 12 days of therapy there was no improvement in the child's clinical condition, and the blood and stool cultures continued to show S. typhosa. In case 6 the patient was treated for the first four days of her illness with sulfadiazine without any improvement, despite complete inhibition of the organism in vitro by therapeutic concentrations of the drug. It is interesting to note that the varying sensitivity of the organisms to chloramphenicol was apparently not related to the rapidity of clinical response to the drug.

There were no pronounced toxic reactions to chloramphenicol in our series. The occasional nausea and emesis that occurred did not persist more than 24 hours, and no eruptions were seen at any time. Although all of our patients showed an increasing neutropenia during the course of therapy, in only three patients (cases 2, 6 and 7) did the absolute neutrophil count drop below 1,000. The lowest count occurred in case 2 when, on the twelfth day of therapy, the leukocyte count had fallen to 3,750, with 12 per cent neutrophils, an absolute count of 450. No bone marrow examination was performed, but eight days after therapy was discontinued the neutrophils had risen to 44 per cent despite the fact that the leukocyte count was still 3,800. In case 7 a bone marrow study made after 14 days of therapy failed to reveal any depression of the myelocytic elements. At this time the peripheral blood showed 4,300 leukocytes, with 16 per cent neutrophils, an absolute count of 688. In this connection, it is interesting to note that Volini and coworkers [21] have recently reported definite evidence of depression of the granulocytes in the bone marrow in three consecutive cases of typhoid treated with chloramphenicol. However, in all three cases there was a prompt rise in the granulocytes after therapy was discontinued.

The consensus at present is that chloramphenicol is the drug of choice in the treatment of typhoid. Other drugs have been found ineffective. However, Brainerd and associates [22] obtained satisfactory results with aureomycin in two children, but seven adults in their series failed to respond. We used penicillin and the sulfonamides without any evidence of improvement in our first cases; others have tried aureomycin and aerosporin (polymyxin B) with little success.[23] In 11 cases of typhoid in children treatment has not been followed by relapses, carrier states or fatalities.[24] On the other hand, numerous instances of relapses have been

21. Volini, I. F.; Schwartz, S. O.; Greenspan, I.; Ehrlich, L.; Gonner, J. A., and Felsenfeld, O: Hemopoietic Changes During Chloromycetin Administration, Proc. Central Soc. Clin. Res. **22**:74, 1949.

22. Brainerd, H.; Lennette, E. H.; Meiklejohn, G.; Bruyn, H. B., Jr., and Clark, W. H.: The Clinical Evaluation of Aureomycin, J. Clin. Invest. **28**(pt. 1):992-1005 (Sept.) 1949.

23. Knight, McDermott and Ruiz-Sandrez.[6] Schoenbach.[12b] Woodward, Smadel and Ley.[16]

24. Stiller.[11] Erickson.[18a]

reported in adults.[25] Smadel [2] found that relapses did not occur if treatment was prolonged for more than nine days. Schoenbach [12b] and Collins,[17] however, reported relapses after 14 days of therapy.

Further doubt as to the value of chloramphenicol in the treatment of typhoid in adults is expressed by the numerous authors who have failed to eradicate the infection in chronic carriers.[26] It has also been shown by Ross [15] that in the treatment of Salmonella infections other than typhoid in infants clinical cure was readily obtained with chloramphenicol but the organism reappeared in the stool after 33 days in seven of nine cases. From the laboratory point of view, Seligmann and Wasserman [27] have found that although chloramphenicol exerted a marked inhibitory effect on the growth of S. typhimurium in vitro, it failed, even in large amounts, to control infection by these organisms in mice.

Despite these facts and the suggestion in a recent editorial of the *New England Journal of Medicine* [28] that under certain circumstances the Salmonella organisms may be inaccessible or in some way protected from the action of chloramphenicol, we feel justified in concluding at the present time that a diagnosis of typhoid in a child warrants the immediate administration of chloramphenicol in adequate doses.

SUMMARY

Seven proved cases of typhoid in children (aged 3 to 6 years) observed during 1949 were successfully treated with chloramphenicol. Diagnosis was confirmed by blood and stool cultures positive for S. typhosa and by typhoid H and O agglutination tests. Three of the cases were severe, three were moderately severe and one was relatively mild. The dose ranged from 0.070 to 0.140 Gm. per kilogram per 24 hours. The duration of therapy was from 10 to 18 days, with an average of 13.9 days. The in vitro sensitivity of the seven strains of S. typhosa isolated ranged from 2 to 4 micrograms per cubic centimeter.

No relapses or significant reactions to therapy were observed. However, most patients showed a significant drop in total leukocyte and absolute neutrophil counts during therapy. The lowest leukocyte count was 3,750 per cubic millimeter, with 12 per cent neutrophils, 75 per cent lymphocytes and 13 per cent monocytes. The leukocyte counts rapidly returned to normal after cessation of therapy.

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ABSTRACT OF DISCUSSION

DR. RALPH V. PLATOU, New Orleans: Since Woodward's preliminary report concerned with typhoid in adults, to which Dr. Greengard and his colleagues have alluded, a number of us around the country have had occasion to be very happy with the results of treatment of typhoid with chloramphenicol. I should like to congratulate Dr. Greengard on the excellence of his observations and add a few others to confirm them.

My colleagues and I have treated nine children with fairly early proved typhoid. All of these have responded satisfactorily. None have relapsed, and none have had complications, save one child who had transient and equivocal evidences of myocarditis.

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25. Schoenbach.[12b] Woodward, Smadel and Ley.[16] Collins and Finland.[17] Briggs.[18b]

26. Smadel, Woodward and Bailey.[2] Bradley.[8] Lomax.[9] Collins and Finland.[17]

27. Seligmann, E., and Wasserman, M.: Action of Chloromycetin on Salmonella, Proc. Soc. Exper. Biol & Med. **71**:253-255, 1949.

28. Chloromycetin in Typhoid Fever and Other Salmonella Infections, editorial, New England J. Med. **242**:191 (Feb. 2) 1950.

eve that the response to therapy with chloramphenicol is so characteristic in the of cases that a physician in a rural area, without laboratory facilities, would stified in attaching a great deal of significance, as a therapeutic test, to a the critically febrile state to apparently complete well-being in about 3½ d tovement is striking in the first 24 hours, and the vast majority of patients are ell and afebrile, apparently completely normal, in 3½ to four days.

no evidence of toxicity due to the drug in the patients we have treated. I would like to ask Dr. Greengard if the rather remarkable granulocytopenia which he observed was perhaps better explained by the natural course of the disease, with suppression of formed elements in the marrow cells and peripheral blood, simply a matter of timing? In other words, was the improvement on cessation of drug administration due to timing rather than to withdrawal?

We have seen similar suppressions in three of our cases. These suppressions were all very transient and unaccompanied with any systemic symptoms of concern to us, and the patients all recovered promptly; we did not believe that the granulocytopenia was in itself an indication for stopping the medication.

The authors should be congratulated for their observations concerning the phage typing of the organisms they encountered. I should like to ask if this technic has been useful in study of carrier states.

DR. EDWARD B. SHAW, San Francisco: I have enjoyed this paper and the opportunity to discuss it. These observations add to the accumulated evidence that chloramphenicol is at the present time the best available drug for the control of typhoid.

Fairly large doses of the drug are required for the control of this disease. The sensitiveness of this organism to chloramphenicol is not so very great when compared with the sensitiveness of some other organisms to antibiotic agents successfully employed in treatment. S. typhosa is not much more sensitive to chloramphenicol than to aureomycin or, sometimes, to streptomycin. Nevertheless, its value in therapy is much greater than laboratory studies would seem to indicate.

Perhaps it is necessary that the effect of the antibiotic be augmented by some physiological cellular response on the part of the patient. Improvement seems to commence in typhoid before organisms have disappeared from the stool or even, in many cases, from the blood culture. This is a finding which is not usual in some other infectious conditions in which there is prompt clinical response to antibiotic therapy. In most of these other diseases improvement occurs only after viable organisms have been greatly reduced or completely destroyed, but in typhoid clinical improvement begins before the number of organisms has been greatly reduced.

Further evidence of the cellular participation is afforded by the white cell count, which seems to remain higher than that usual in typhoid in the course of successful therapy while there are still many organisms in the blood stream and bowel.

The carrier state seems not to have been nearly so well controlled by the use of large doses of chloramphenicol as the active clinical disease. For the treated carrier one or two cultures negative for S. typhosa seem frequently to be succeeded by a later positive one, with the very definite suspicion arising that if successive cultures were continued long enough in any given series, cultures positive for S. typhosa would frequently finally be detected. Cultures positive for S. typhosa will especially be obtained after the use of saline cathartics, which bring the gallbladder content quickly through the intestinal tract. Conversely, cultures which do not show pathogens are much more likely to be found for the constipated patient.

One possible reason for the value of chloramphenicol in the treatment of typhoid, as compared with other drugs to which the organism is equally sensitive in the laboratory, may lie in the better absorption of this drug from the lower part of the intestinal tract. Chloramphenicol has been shown to be well absorbed with rectal administration, in contrast to aureomycin, for which rectal absorption was extremely poor.

It is interesting to note that in these cases of patients successfully treated for typhoid other organisms such as Pseudomonas and Proteus, which are also pathogenic, were found in the stools in high concentration. We do not know all the end results of antibiotic therapy, and it may well be that when we have eradicated some of the major offenders in this bacterial warfare, we may still have a few guerrillas which we will have to clear up. Many illustrations of this will come

to mind; there is a certain balance of nature among micro-organisms. The principle may become more important as experience with these agents accumulates.

DR. WILLIAM A. REILLY, Little Rock, Ark.: It gave me pleasure to listen to this paper and compare it with our experience for the past year in Little Rock, where my colleagues and I have had the opportunity to treat some 15 patients in the past 10 months; there is a report of this treatment (*J. Pediat.* **36**:440 [April] 1950).

I should like to comment briefly on some of our cases. We feel that most of our typhoid comes from carriers. The health department has searched vigorously and cannot find it in food or water sources.

Clinically we are getting out of "touch" with the natural course of this disease, especially as regards the complications and sequelae, because of successful treatment. When we encounter fever, diarrhea and leukopenia, we immediately rule out typhoid.

The doses that we used were 50 mg. per kilogram initially followed by 125 mg. for smaller or 250 mg. for larger children every four to six hours until the temperature was normal for five to seven days. The temperature returns to normal in 3½ to four days, as Dr. Greengard and Dr. Platou mentioned. We have had one remission. That was due to stopping treatment too early when we first employed the drug, owing to lack of the drug. We have not seen any ill reactions. We have not seen any complications from the disease since chloramphenicol was used. I think it is a great boon in the Southland, for we still see typhoid, not rarely. Communicable diseases are dying out down there also.

DR. JOSEPH GREENGARD, Chicago: I should like to stress one or two things that have been said by the discussants.

With regard to this matter of granulocytopenia, I feel very much as Dr. Platou feels, that it is merely a manifestation of the disease. However, Volini and Schwartz came out with their report rather quickly last winter in which they maintained that they found a hypoplastic marrow in patients with granulocytopenia. In our case we found a full marrow and absolutely no evidence of impairment of production of granulocytes.

In regard to phage typing in carrier states, I might mention that these phage typings were done for us by the Illinois State Department of Health. They used the method very extensively in the detection of carriers.

So far as in vitro studies and their not agreeing with the experience in the patient are concerned, I think that should be stressed, too. We found the organisms we obtained in these cases almost universally sensitive in the test tube to sulfathiazole and sulfadiazine and very frequently sensitive to aureomycin. Still, in the patient none of these drugs were effective.

PNEUMATOSIS INTESTINALIS IN THE NEWBORN

O. ARTHUR STIENNON, M.D.
ANN ARBOR, MICH.

SINCE the roentgen appearance of pneumatosis intestinalis, or intestinal emphysema, in children has not previously been reported, the following two cases are recorded.

REPORT OF CASES

CASE 1.—S. C. was the second born of premature twins delivered on Jan. 11, 1950 at about seven months of gestation. After discharge from the hospital the patient did not eat well and was readmitted for premature care, at which time he had up to 12 loose green stools a day. There was no vomiting. On readmission on February 9 the patient still had diarrhea and refused to eat. At that time he weighed 4 pounds 12 ounces (2,155 Gm.). He was dehydrated and cyanotic, with stippling of the skin of the trunk. On February 16 he began to have abdominal distention, vomited bile and had several bloody mucous stools.

A scout film of the abdomen (fig. 1 *A*) showed gaseous distention of the colon and a spectacular radiolucent stripe outlining the greater portion of the colon on all its margins. There were two or three loops of distended small bowel in the midabdomen. In the region of the junction of the sigmoid with the descending colon there was a sharp indentation thought to be due to transitory spasm.

The radiolucent stripe described above was thought for several reasons to be due to air in the plane between the mucosa and the other layers of the bowel wall and to represent a condition known as pneumatosis intestinalis. One of the reasons is that at no point does the homogeneous material, which appears to be bowel contents, actually come in contact with the outer margin of the radiolucent stripe, as certainly would be expected in the case of fecal material surrounded by gas. Furthermore, at one point where the colon is empty of fecal material and contains only gas a thin stripe of increased density is seen between the gas in the colonic lumen and the outlining radiolucent stripe. In lateral projection (fig. 1 *B*) one loop appears to be completely surrounded by gas, and the appearance is that of a ring of increased density surrounded on both sides by radiolucent shadows.

The fact that the typical meshlike or cystic accumulations of gas described in the literature are not seen here may be accounted for by the ease with which the mucosa is stripped from the remaining layers of the intestine in a person of this age. The general appearance of the radiolucent stripe suggests that the gas is arising from a point near the sigmoid-descending colon junction and spreading in a more proximal direction.

Surgical exploration (Dr. M. A. Hayes) showed the entire colon to be diffusely infiltrated with gas. The gas, which was apparent subserously and intramuscularly, crepitated on palpation. Similar gaseous infiltration was detectable in the transverse mesocolon and appeared to extend into the root of the mesentery and diffusely into the mesenteric attachment of the small bowel. Many portions of the small bowel were similarly affected by the gaseous infiltration.

A colostomy was done for decompressive purposes. A portion of the proximal ileum was obviously nonviable and was resected, and an end to end anastomosis was done.

Four days later a second scout film of the abdomen showed complete disappearance of the gas. At that time there was homogeneous obscuration of the entire abdominal area, suggesting ascites. There also was widespread, patchy increased density throughout the right lung.

The patient died on February 21. The following are the anatomic diagnoses. There were severe confluent aspiration, lobar pneumonia and multiple old pulmonary infarcts. The small

From the Department of Roentgenology, University of Michigan, Ann Arbor, Mich.

intestine showed severe congestion. There were hemorrhagic and anemic infarction; marked edema and hemorrhage between the muscularis mucosae and muscularis propria; leukocytic infiltration throughout the wall; fibrinopurulent peritonitis; purulent thrombi or emboli in mesenteric veins, and pneumatosis intestinalis.

The colon showed chronic catarrhal colitis. There were subacute fibrinopurulent peritonitis in the region of the colostomy and necrosis of the entire wall at one end of a specimen.

Microscopically the gas cysts were located between the muscularis mucosae and the muscularis propria. The involvement was so extensive that the bowel specimens were still floating in the fixative three months after death. There were inspissated bile in the liver canaliculi and marked degenerative fatty infiltration of the liver.

Forfota [1] has stated that "pneumatosis intestinalis is so rare a disease that most clinicians and roentgenologists never see a case in their entire lives." Nevertheless, S. C. and the patient in the following case were in the nursery at the same time!

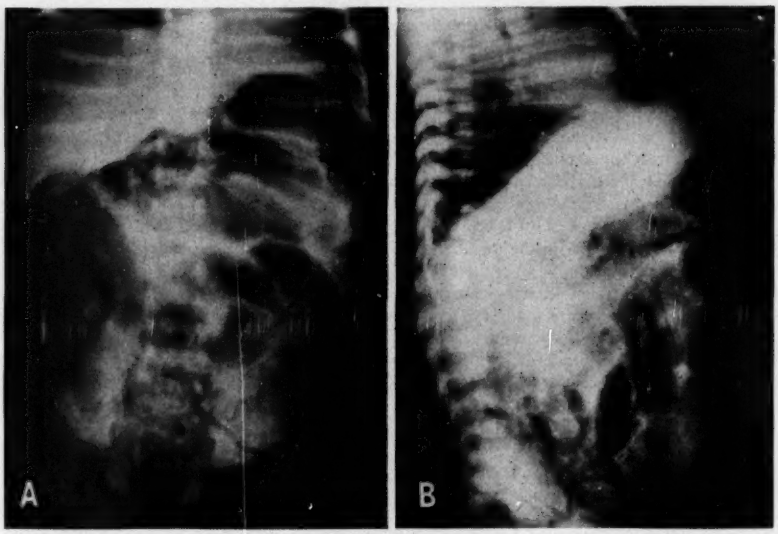

Fig. 1 (case 1).—The radiolucent zone outlining the lower colon might easily be taken for gas surrounding impacted feces. At no point, however, does the granular column come in contact with the dense areas outside the radiolucent zone—not even at the junction of descending and sigmoid colon where there is a sharp indentation. The material inside the stripe proved to be mucosa so inflated it resembled a piece of absorbable gelatin sponge. Several double ring shadows are seen in *B*. Note the gas in perirenal tissues.

Case 2.—M. K., a full term infant, aged 3 days, was admitted on Feb. 17, 1950 with the diagnosis of esophageal atresia and tracheoesophageal fistula below the level of obstruction. A gastrostomy was performed on February 18, and on February 19 repair of the fistula and end to end anastomosis of the esophagus were done (Dr. Cameron Haight).

On February 23 the infant had bloody stools as well as regurgitation of bowel contents through the gastrostomy.

On February 21 an abdominal scout film (fig. 2) showed in the left upper quadrant and descending into the left lower quadrant at least three loops of bowel which had the typical

1. Forfota, E.: Die Pneumatosis cystoides intestini im Röntgenbilde, Fortschr. Geb. Röntgenstrahlen **53**:131, 1936.

ringlike configuration with a radiolucent bowel lumen, radiopaque bowel mucosa and in the periphery a radiolucent stripe so characteristic of pneumatosis intestinalis. The stomach was markedly distended by gas. There were multiple gas-filled loops of large bowel and small bowel. No gas was seen in the rectum. There was also gas in the soft tissues of the thigh on the right and in the retroperitoneal tissues along the right lateral abdominal wall. A small pocket of gas was seen in the region of the right inguinal canal.

Because of a question of intestinal obstruction, suggested by abdominal distention and bloody diarrhea, the lower bowel was investigated by injecting a mixture of iodized oil U. S. P. (lipiodol®) and liquid petrolatum rectally. As oil ascended it fully ballooned the rectal ampulla. The ascending colon and sigmoid were never fully distended, and their margins were grossly

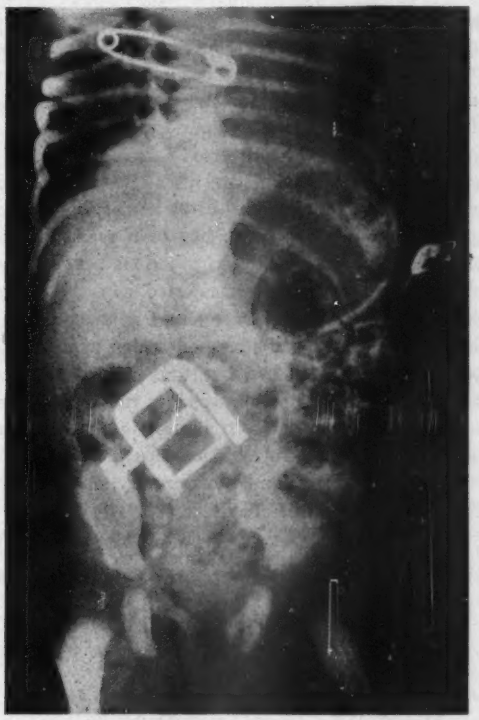

Fig. 2 (case 2).—The ring within ring shadow of the inflated bowel as seen in cross section is characteristic. The stomach is distended despite the gastrostomy tube. After suction was applied to the gastrostomy tube all evidence of pneumatosis vanished within 12 hours.

and constantly irregular, suggesting that there were emphysematous cysts in the mucosa of the descending colon as well. After some difficulty a point at the junction of the splenic flexure and descending colon was reached. At this level it was observed that gas bubbles passed down through the column of contrast medium and were discharged through the rectum. This was taken as convincing evidence that no intussusception existed.

A conservative attitude was advised by the surgical consultant. Because of the evidence of distention of the stomach and signs of intestinal obstruction, suction was applied to the gastrostomy tube. A scout film 12 hours later showed complete disappearance of the interstitial air. However, despite administration of fluids, plasma, and the like, the infant became progressively dehydrated and died on March 10. Permission for autopsy was not obtained.

HISTORY

The first account of this condition is usually attributed to Bang,[2] who reported an autopsy case in 1876. It seems, however, that earlier accounts of the condition were in existence, namely, Mayer's [3] description in 1825 of the disease in swine and the still earlier report (1730) of the anonymous Russian author I. G. D., cited by Combalousier. It is not known whether this description applied to a specimen from a human subject.

Priority would ordinarily go to Cloquet [4] (1820) were it not for the remote possibility that the changes he reported were due to postmortem changes.[5]

The first American case is sometimes credited to Finney,[6] but the condition had been reported prior to this by Barry.[7] The early cases were diagnosed only at autopsy. Hahn [8] (1899) appears to have been the first to make the diagnosis intra vitam, in a patient operated on for pyloric obstruction. Incidentally, the outcome of this first operative case was initially successful.

Maass,[9] in 1904, described the first reported case in a child. This concerned a 7 month old boy initially treated for a chylous ascites of unknown cause. The diagnosis of pneumatosis was first established at autopsy, although the immediate cause was not apparent until the specimen had been reexamined by Benda, who discovered an indurated, canal-like orifice in adhesions between the omentum and the postero-inferior gastric wall which connected a mass of gas cysts in the omentum with the stomach lumen. Pressure on the stomach inflated the cysts, and the cysts could be deflated by manual pressure, which apparently caused the gas to reenter the stomach. Moreau,[10] as early as 1917, predicted that eventually a preoperative diagnosis would be made on the basis of the roentgenologic appearance of the abdomen. Reverdin [11] was able to fulfil this prophesy in 1924, and his diagnosis was confirmed by laparotomy. Since then the diagnosis has been made occasionally,[12] usually with confirmation by exploratory laparotomy. The condition has never been detected in a child before death.

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2. Bang: Nord. med. Ark. **8**:18, 1876.

3. Mayer (Bonn): Beobachtung einer Pneumatosis cystoides intestinorum, Hufelands, S. J. pract. Heilk. **61** (pt. 2):67, 1825.

4. Cloquet, J.: Bull. Fac. méd. Paris Séance 7, 267 (Aug. 3) 1820.

5. Nitch, C. A. R., and Shattock, S. G.: Diffuse Emphysema of Intestinal Wall (2 Cases) with Remarks upon Pneumatosis, Proc. Roy. Soc. Med. **12**:46, 1919.

6. Finney, J. M. T.: Gas Cysts of the Intestine, J. A. M. A. **51**:1292 (Oct. 17) 1908.

7. Barry, cited by Engstad, J. E.: Journal-Lancet **42**:565, 1922.

8. Hahn, E.: Über Pneumatosis cystoides intestinorum, Deutsche med. Wchnschr. **25**: 657, 1899.

9. Maass, H.: Demonstration eines Preparates von Emphysema des grossen Netze, Berl. klin. Wchnschr. **41**:401, 1904.

10. Moreau, L.: Sur un cas d'hépatoptose par interposition avec kystes gazeux de l'intestin, Arch. électr. méd. **27**:393, 1917.

11. Reverdin, A.: Maladie kystique de l'intestin, Rev. méd. Suisse Rom. **44**:546, 1924.

12. (*a*) Frostberg, N.: Pneumatosis cystoides intestini: Contribution to Casuistics, Acta radiol. **29**:521, 1948. (*b*) Gazin, A. I.; Brooke, W. S.; Lerner, H. H., and Price, P. B.: Pneumatosis Intestinalis, Am. J. Surg. **77**:563, 1949. (*c*) Lerner, H. L., and Gazin, A. I.: Pneumatosis Intestinalis, Am. J. Roentgenol. **56**:464, 1946. (*d*) Røjel, K.: Un cas de pneumatose kystique intestinale diagnostique par la rectoscopie, Acta chir. Scandinav. **97**:276, 1948.

From the extensive reviews of the literature[13] it appears that approximately 180 cases have been reported, of which 12 have been in children.[14] Perhaps 25 cases have been reported since Ferrandu's review in 1935.

CLINICAL OBSERVATIONS

Pneumatosis cystoides intestinalis may be defined as an abnormal collection of gas in the walls of the intestine or its supporting structures. Predilections for the terminal ileum, ascending colon and jejunum have been described,[15] but these are not striking. A high percentage of the cases reported have been associated with pyloric stenosis, pyloric ulcer or both. The stomach is occasionally affected,[16] but the duodenum is invariably spared even though the rest of the small bowel is extensively involved.[17] When the small bowel is involved, there appears to be a predilection for the mesenteric border, although this is far from the rule.[18] The cystic accumulation of gas may be found between any of the bowel layers, although it is seldom encountered in the space between the longitudinal and circular muscular layers. In children, although an occasional subserosal cyst may be found, the major portion of the gas is invariably[1] in the submucosa. In adults, both locations are frequently involved, but the most striking abnormality is usually subserosal.[5] Accumulations of gas cysts are also frequently encountered in the mesentery and omentum. The most curious finding has been the association of emphysematous blebs in the vaginal mucosa.[19] As early as 1820 Cloquet[4] found gas cysts in the gastrohepatic ligament, gallbladder and omentum. No definite connection has been established with the occasional finding of emphysema of the urinary bladder.

In children the incidence of gastric pathologic condition is not as striking—only the patients of Maass[9] and Botsford[14c] had obvious gastric abnormality. Vomiting and diarrhea have been the two most frequent symptoms; melena and hematemesis (Moore,[14b] case 1) have each been reported once. In most of the cases in children the first diagnosis was upper respiratory tract infection or pneumonia. Nephrosis, jaundice, edema and ascites have been associated findings. Gas in the lymphatics, while a rare finding in adults,[20] has been found in a majority

13. (*a*) Turnure, P. R.: Gas Cysts of the Intestine, Ann. Surg. **57**:811, 1913. (*b*) Mills, H. W.: Gas Cysts of the Intestine Cistica, Surg., Gynec. & Obst. **40**:387, 1925. (*c*) Memmi, R.: Un caso di pneumatosi intestinale, Policlinico (sez. chir.) **41**:408, 1934. (*d*) Ferrandu, S.: studio anatomo-patologico e interpretazione patogenetica della pneumatosi intestinale cistica, Arch. sc. med. **60**:493, 1935.

14. (*a*) Schnyder, K.: Zur Lehre der Pneumatosis cystoides intestini hominis, Cor.-Bl. schweiz. Aerzte **47**:289, 1917. (*b*) Moore, R. A.: Intestinal Pneumatosis, Am. J. Dis. Child. **38**:818 (Oct.) 1929. (*c*) Botsford, T. W., and Krakower, C.: Pneumatosis of the Intestine in Infancy, J. Pediat. **13**:185, 1938. (*d*) Lindsay, J. W.; Rice, E. C., and Selinger, M. A.: Pneumatosis Cystoides Intestini in an Infant, Arch. Path. **30**:1085 (Nov.) 1940. (*e*) Maass.[9]

15. Silverstone, J.: Cystic Pneumatosis of Bowel, Lancet **1**:129, 1928.

16. Dupraz, A.: Sur l'emphysème spontané, Arch. méd. exp. **9**:282, 1897.

17. Nitch and Shattock.[5] Forfota.[1]

18. Nigrisoli, B.: Sulle cisti gasose dell'intestino umano, Nuovo racc. med. **1**:385, 1902. Miyake, K.: Über Pneumatosis cystoides intestini, Arch. klin. chir. **95**:429, 1911. Mori, M.: Nachtrag zu dem Fall von "Pneumatosis cystoides intestinorum hominis," Deutsche Ztschr. Chir. **88**:553, 1907; ibid. **91**:620, 1908. Turnure.[13a] Silverstone.[15]

19. Eisenlohr, W.: Der Pneumatosis intestini, Beitr. path. Anat. **3**:101, 1888. Jager, H.: Das Vaginal- und Intestinalemphysema, Verhandl. deutsch. path. Gesellsch. **10**:251, 1906.

20. Urban, H.: Anatomische und röntgenologische Befunde bei der Pneumatosis cystoides intestini, Fortschr. Geb. Röntgenstrahlen **55**:231, 1947.

of the 12 cases in children. In Botsford's second and third cases the cisterna chyli and thoracic duct were distended by gas. This may be related in some way to the fact that the gas is invariably in the submucosa in children. In Urban's case of an adult with gas in the lymphatics the gas was originally submucosal, from roentgen evidence (discussed below).

PATHOLOGY

Two microscopic pictures have been described. In the first of these the cysts appear as unlined cavities formed by the separation of the muscularis mucosae and muscularis propria or separation of the serosa from the underlying bowel. Small hemorrhages into these spaces and, more frequently, accumulation of an albuminous exudate in them have been described.

A more commonly found description is that of an air-filled cavity lined by a thin layer of "endothelium." Multinucleated giant cells are found within the lumen.[21] Some dispute exists as to whether these are foreign body giant cells or not.[14d] In cases presenting these cells the walls of the cyst are often thick and composed of many layers of fibrous tissue.

In those instances in which the duration of the disease has been definitely established (by previous operation, as in the case of Korte,[22] or by the length of life of infants) the cysts have been unlined and few or no giant cells were seen. Fibrotic walls were not found in these cases. From this it seems apparent that these two pathological pictures can be reconciled as different stages in the same disease. It appears that the first description is applicable to the case of pneumatosis of recent origin and that the fibrosis, "endothelial" lining and giant cell formation occur in more chronic cases and represent a reaction to the gas and the mechanical tensions which it creates.

ETIOLOGY

The exact mechanism by which the emphysema is produced is still debatable. Of merely historical interest is the explanation given by Mayer,[3] who was one of the first to report the disease in swine. This author reasoned by analogy from a case reported by Giroud [23] in 1774. Giroud's case was concerned with a hydatidiform mole, the cysts of which were partially air containing. Giroud explained this unusual feature by postulating that the fluid within the cysts had been resorbed and the dissolved gases of the fluid had remained within the cyst. It was Mayer's opinion that a similar explanation could account for pneumatosis of the intestine.

Bang is responsible for the "tumor theory" suggested by his finding of giant cells in the cysts. As late as 1919, Finney, working with the pathologist Welch, was of the opinion that pneumatosis intestinalis was a true neoplasm, the cells of which secreted gas. At this time the possibility of cells secreting a gaseous product was still unrefuted. Ample evidence exists to contradict this conception founded on the presence of air bladders in fish. It has been shown that the analogy with the fish air bladder is a false one on histological grounds because of the absence of any

21. Masson, P.: La lymphopneumatose kystique, Ann. anat. path. **2**:541, 1925. Jackson, J. A.: Gas Cysts of the Intestine, Surg., Gynec. & Obst. **71**:675, 1940.

22. Korte, in discussion of paper by Hahn, Deutsche med. Wchnschr. **25**:255 N. R. 42, 1899.

23. Giroud: J. méd. **17**:1774; cited by Mayer.[3]

intracellular gas. Moreover, when the duration of the disease is known to be short, a well developed endothelial or epithelial lining has not been present, nor have the giant cells, to which the secretion was attributed, been found.

The bacterial theory has from time to time been enthusiastically endorsed, despite the failure of observers to find micro-organisms in the cysts consistently. Even when bacteria were found, these were often not gas-forming organisms.

At least in adults the most convincing argument against a bacterial origin of this condition is the relatively benign course of the disease—in sharp contrast to the usually fatal outcome of infections by gas-forming organisms elsewhere. Histologically, bacteria are seldom found in the cysts, and inflammatory changes are in the background. Analyses of the gas contained in these cysts have been variable, but in general the composition of the contained gas is approximately that of atmospheric air.[24] This, too, is an objection to a bacterial origin of the gas, inasmuch as the gas produced by micro-organisms contains a high percentage of carbon dioxide and very little, if any, oxygen.

The theory of pathogenesis to which most modern authors subscribe is a mechanical one. According to this theory, the air gains entrance to the submucosal and subserosal surfaces by way of ulcerations in the bowel mucosa and advances from this initial localization in much the same way as a dissecting aneurysm, by creating planes of cleavage.

The mechanical theory in its present form can be criticized from several points of view in that (1) it explains only one thing: the fact that air is in the interspaces of the bowel; (2) it does not explain many things, for example, the association of pneumatosis with pyloric obstruction, the invariable sparing of the duodenum, the "skip" areas of involvement along the course of the small bowel and such occasional findings as involvement of the colon and complete sparing of the small bowel in those patients with pyloric stenosis and ulceration; (3) a new assumption must be made to explain each of the peculiarities of the disease, and (4) it provides a false rationale for treatment. Each of the above points will be considered in more detail.

There can be no doubt that a small rent in the mucosa provides a possible entrance for gas. That gas actually does enter in this way is more difficult to accept. Proponents of this explanation are wont to postulate gas under increased pressure in the intestinal lumen to provide the not inconsiderable force which must initiate the dissecting process. There is no ground for assuming this, and all evidence points to the opposite conclusion. In adults, who comprise the majority of patients, intestinal obstruction is rare, and when it does occur it is usually the result, rather than the cause, of the gas cysts.[2] Even if this assumption is admitted, it is difficult to see why the pressure of the gas in the lumen should not press the flabby mucosa against the more resistant muscularis and effectively seal the rent. Experiments which more or less reproduce the condition by injection of the submucosa through a rigid needle[5] are not regarded as a reproduction of the mechanics of the disease.

To give pyloric stenosis the causal significance it must have in view of its high incidence among patients with pneumatosis, it is necessary either to assume that it produces an ulcerated colon and small bowel, which in turn leads to the gas cysts

24. Moore.[14b] Nitch and Shattock.[5]

as described above, or to make the more reasonable assumption that the gas comes from the stomach. In the latter case it has been impossible to explain the sparing of the duodenum without making the additional assumption that it is missed at postmortem examination or that "a different type of peristaltic activity in the duodenum" prevents pneumatosis from developing.[12e] Incidentally, this explanation breaks down when one attempts to apply it to jejunal and ileal "skips" or to the passing over of the entire small bowel in favor of the colon. The bowel cannot reasonably be supposed to be made up of segments alternately endowed with peristaltic activity favorable or unfavorable to the development of pneumatosis.

To assume that a highly improbable disease rises independently three or four times in the same person is also unwarranted, and for this reason the possibility of pyloric stenosis producing an ulceration of the intestinal mucosa of a type which favors the entrance of gas can be safely ignored.

Unfortunately, the mechanical theory in its present form does point to a primary deficiency, which naturally leads to surgical attempts at cure aimed at the "cause." This has resulted in the resection of as many as 14 feet (427 cm.) of involved bowel (Englund, 5 feet [152 cm.]; Demmer,[25] 80 cm.; LaFourcade, 14 feet; Gazin, 14 feet). This seems unwarranted, as cures have been reported from surgical procedures ranging from puncture of a few of the cysts or biopsy [8] to simple gastrojejunostomy. In individual instances resolution of the cysts has occurred after an exploratory laparotomy at which no surgical procedure was done.[20]

A NEW MECHANICAL THEORY

Any theory which attempts to explain the development of pneumatosis must provide a reasonable explanation of the following observations:

1. Pneumatosis is frequently associated with pyloric obstruction and ulceration. Faltin [27] gives an incidence of 55 per cent; Kopelowitz,[28] 45 per cent; Hey,[29] 62 per cent, and, most recently, Ferrandu,[18d] 72 per cent. This incidence is far too high to be compatible with an accidental association of the two findings. The percentage of all laparotomies performed for relief of pyloric obstruction is certainly much lower than any of these figures.

2. In general, the outcome in adults is favorable, with either spontaneous resolution [20] or cure after what may be considered inadequate therapy (Cristol and Porte, exploratory laparotomy; Mills's second case, appendectomy).

3. Curiously, despite the high incidence of associated pyloric disease, the duodenum is invariably spared.

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25. Demmer, F.: Zur Kenntnis der Pneumatosis cystoides intestini hominis, Arch. klin. Chir. **104**:402, 1913.

26. Cristol and Porte: Les kystes gazeux de l'abdomen, Presse méd. **27**:726, 1919. Barjon, F., and Dupasquier, D.: Kystes gazeux de l'intestin, Lyon méd. **71**:565, 1913.

27. Faltin, R.: Zur Kenntnis der Pneumatosis intestini, Deutsche Ztschr. Chir. **131**:166, 1914.

28. Kopelowitz, M.: Zur Kenntnis der Pneumatosis cystoides intestinorum hominis, Arch. Path. Anat. **248**:369, 1924.

29. Hey, R.: Über Pneumatosis cystoides intestini hominis, Deutsche Ztschr. Chir. **154**: 250, 1920.

4. Equally curiously, there is a tendency for the disease to "skip." In Mauclaire's [30] case three such "skips," with uninvolved segments of jejunum 10 cm. or more in length, were noted. Pybus [31] noted five "skips"; in Kadyan's [32] case the cysts were on either end of a 1 meter segment of normal bowel. Lejars' [33] case of pneumatosis with pyloric ulcer and obstruction showed gas cysts of the colon with complete sparing of all segments of the small bowel. Many similar cases could be mentioned.

It would also be desirable if such a theory would explain the predilection for the mesenteric border of the intestine as a site for cysts and the difference in appearance and distribution of the condition as seen in the newborn. Such a theory should provide a rationale for treatment, explain the possibility of rapid resolution and account for the composition of the gas.

Initial assumptions which are self evident may now be made: (1) there must be a supply of gas and (2) the gas must be under pressure. This combination of circumstances—gas under pressure—is found normally only in the stomach, duodenal bulb, terminal ileum and colon. From this it can be immediately deduced that the gas must arise from one of these sites. First to be considered are the stomach and the duodenum.

In 72 per cent (Ferrandu) of 146 cases in which the information was available the region of the pylorus and duodenal bulb was involved in an ulcerating process, usually with pyloric stenosis. In three of these cases the obstruction at the gastric outlet was due to carcinoma of the stomach. In these cases of associated pyloric disease one can postulate that gas under pressure in the stomach escapes from the gastric lumen by way of an ulcer which penetrates in such a fashion as to allow gas to escape between the layers of the gastrohepatic or hepatoduodenal ligaments. If the greater curvature is the site of the penetrating ulceration, the gas can escape into the layers of the omentum. That such is the case was demonstrated by the observations of Maass and Benda, who found a direct communication between the gas cysts and the stomach lumen in the form of a well defined indurated channel.

Although direct evidence of such a channel communicating with the space between the layers of the hepatogastric or hepatoduodenal ligaments is lacking, considerable indirect evidence exists. Inasmuch as the common bile duct lies in the hepatoduodenal ligament, one could anticipate biliary symptomatology due to obstruction. Such obstructive jaundice was found in the case of Lindsay, in Botsford and Krakower's case 2 and my case 1. In several other cases (Botsford, cases 4 and 5) biliary cirrhosis of unspecified type was found.

Gas has actually been found in the gastrohepatic ligament by Stori [34] (case 1), Engstad [35] and Cloquet.[4] Another possible site of extension from this initial focus is into the falciform ligament. Gas in this location has been reported by Pybus.

30. Mauclaire, M.: À propos des kystes gazeux de l'intestin, Bull. et mém. Soc. chirurgiens Paris **65**:1334, 1919.

31. Pybus, F. C.: A Case of Gas-Cysts of the Intestine, Brit. J. Surg. **21**:539, 1934.

32. Kadyan: Pneumatosis cystoides intestinorum hominis, Russk. Chir. Arch. **18**:1183, 1902, abstracted by Finney.[6]

33. Lejars, F.: La pneumatose kystique de l'intestin, Semaine méd. **33**:517, 1913.

34. Stori, T.: Contributo allo studio delle cisti gassosse dell'intestino umano, Clin. mod., Pisa **10**:481, 1904.

35. Engstad, J. E.: Gas Cysts, Journal-Lancet **42**:565, 1922.

Probably the most frequent extension, however, is to the mesenteric root (fig. 1 *B*), which is in close spatial relation to the above structures. The sparing of the duodenum, the multiple sites of involvement of the small bowel with skipping of segments of small bowel and, indeed, the occasional sparing of the entire small bowel now become obvious. From the mesenteric root one or many tongues of gas can dissect through the mesentery, extend to the mesenteric insertion on the intestine and from here either dissect along the subserosal layers or, following the blood vessels which insert on the mesenteric margin of the intestine, enter the submucosa. Why in any particular instance the sites of involvement should be what they are may be related to the course of larger blood vessels in the mesentery.

In addition to the many cases of "skipping," I should mention in this connection the finding of cysts in the mesentery by Cristol and Porte, Nigrisoli, Langenbuch,[36] Englund and Wahlgren,[37] Turnure and others. An objection to the present mechanism might be that gas cysts in the mesentery are not found invariably. It seems probable that in many cases by the time exploratory laparotomy or postmortem examination are performed, the original channels of communication are obliterated. In addition, it is unlikely that a careful search for such channels has been made, since previously there has been no particular reason to suspect that they should exist. It is also quite likely that such channels have been misinterpreted as lymphatics (as by Letulle[38]). It is most interesting, however, that in some cases[37] long linear strands of scar tissue have been found in the mesentery. It would seem that the present explanation of the genesis of the gas cysts is also successful in explaining this hitherto unaccounted for finding.

Once having reached the mesenteric insertion on the intestine, the gas apparently has an option of extending in the subserosal spaces or, probably following the perforating blood vessels, entering the submucosal space. In individual cases the site of extension is variable, and both routes may be followed. As previously mentioned, in infants there is a predilection for the submucosal spaces. According to the method of extension, two outcomes are possible. If the greater portion of the gas extends into the subserosal layers, no great damage may be done unless the presence of the cysts serves as a stimulus to volvulus formation. Only in rare instances has the gas accumulation outside of the muscular layers been sufficient to cause intestinal obstruction.

If, on the other hand, the greater part of the gas extends into the submucosa, the bowel lumen is easily occluded by the pressure of the gas forcing the two opposing layers of mucosa into contact and thus effectively sealing the lumen. One would expect this mechanism to give rise to symptoms of intestinal obstruction. Here collateral evidence from the peculiarities of the disease as it occurs in children may be cited.

In infants the submucosa is the site of predilection. Hence, we should expect to encounter intestinal obstruction in every case. Of 12 cases in infants, with the exception of that of Maass, the gas was located for the most part submucosally and

36. Langenbuch, in discussion of paper by Hahn: Deutsche med. Wchnschr. **25**:255 N. R. 42, 1899.

37. Englund, F., and Wahlgren, K.: Fall von Pneumatosis cystoides intestinorum beim Menschen, Acta chir. Scandinav. **76**:601, 1935.

38. Letulle, M.: Les kystes gazeux de l'intestin et du peritoine, Presse méd. **78**:781, 1919. Letulle, M., and Tuffier: Gas Cysts in the Abdomen, Bull. Acad. méd. **82**:5, 1919.

invariably was accompanied with intestinal obstruction. This was particularly evident in the two patients reported herein. The outcome of the disease, which in children has been invariably fatal, also fits in nicely with the submucosal location of the air. With stretching and tearing of the blood vessels, the mucosa is rendered practically avascular, and it is doubtful whether any considerable extent of the disease is compatible with healing. On the contrary, subserosal air does not ordinarily interfere significantly with bowel function and generally has a benign outcome.

Apparently when the retroperitoneal route is taken, gas reaches the vaginal mucosa.[19]

Gas cysts have also been found in the gallbladder,[4] mesocolon,[39] peritoneal covering of the kidneys,[13a] lesser pelvis,[40] diaphragm [41] and liver peritoneum.[42]

All of this collateral evidence supports the thesis that in cases of pneumatosis intestinalis associated with gastric or duodenal disease, the gas reaches its diverse situations by retroperitoneal extension from a peptic ulcer.

To account for the disappearance of the gas in 12 hours in case 2, three explanations can be advanced: 1. The gas was absorbed. This seems unlikely, as the layer in which it was deposited was undoubtedly avascular and the time interval is too short. 2. A cyst ruptured, with escape of the gas into the peritoneal space. This too is unlikely, as even a small pneumoperitoneum will not resorb in this short interval and no pneumoperitoneum was found at 12 hours. 3. The gas was aspirated by the suction applied to the stomach. This seems the most probable mechanism and in itself could lead to postulation of the "short cut" via the mesenteric root which has already been deduced from other grounds. Certainly, gas in the splenic flexure of the colon could hardly be aspirated along the entire length of the small bowel.

A similar mechanism probably exists in the colon and terminal ileum where gas is also normally present and periappendical disease and tuberculous enterocolitis are frequent concomitant findings.

The possibility that an ulcer in the small bowel with small bowel obstruction below the site of ulceration can be the source of the gas is not excluded by the present theory. It is, however, difficult to find even one case in which it is clearly demonstrated that small bowel obstruction preceded the formation of the gas cysts.

PROGNOSIS

It is evident from what has been said that the major factor in the prognosis of pneumatosis intestinalis is the location of the gas. Enough has been written to indicate that a relatively good prognosis can be given when the gas is located in the

39. Shennon, T. W., and Wilkie, D. P. D.: Gas Cysts of the Intestine, abstracted by Ferrandu, J. Path. & Bact. **14**:259, 1909. Philip, E.: Ein Fall von Pneumatosis intestinalis bei Appendicitis, thesis for the doctorate, Leipzig, E. Lehmann, 1911, tabulated by Ferrandu.[13d]

40. Vallas and Pinatella: Un cas de kyste gazeux de l'intestin, Lyon méd. **97**:215, 1901.

41. (*a*) Jaboulay, M.: Kystes gazeux de l'intestin, Lyon méd. **96**:753, 1901. (*b*) Ruckensteiner, E., and Kux, E.: Über die Pneumatosis cystoides intestini und die Möglichkeit ihrer röntgenologischen Diagnose, Fortschr. Geb. Röntgenstrahlen **47**:661, 1933. (*c*) Vallas and Pinatella.[40]

42. Ruckensteiner and Kux.[41b] Forfota.[1]

subserosa. Submucosal involvement, on the contrary, must have a more serious outcome. Here the mucosa is deprived of its blood supply, and as a result necrosis, ulceration and eventual perforation can occur. In addition, there are bleeding from the ruptured capillaries into the cysts and bowel obstruction due to distended mucosa occluding the lumen. It is difficult to separate entirely the factors which are responsible for the invariably fatal outcome of the disease in children. On the one hand, the invariable submucosal location of the gas produces an alteration of bowel dynamics and physiology which is only in part reversible. On the other hand, difficulties connected with maintenance of fluid balance and nutrition which might be overcome in adults might be insuperable in infants or very young children; hence, the factors of age and location of the gas to a certain extent overlap.

Several mechanisms are probably in effect to produce a remission of the disease. Sealing of the air leak in the stomach or other affected portions of the bowels, by removing the supply of gas, should shortly lead to cure, since what gas has already been introduced will in the course of time be gradually resorbed. Removal of the head of pressure of gas at the site of origin is probably the chief mechanism of cure. If a gastroenterostomy has been performed, even though the initial channel for escape of the gas may persist for some time, the absence of intragastric tension will remove one of the causative factors.

Surgical rupture of a number of cysts creates a free channel for escape of the gas. Once in the peritoneal cavity, the gas can be resorbed by the usual mechanism; and if at the same time healing of the ulcerated bowel or stomach occurs, the condition should clear up.

The blebs may rupture spontaneously, with production of a pneumoperitoneum.[43]

A natural channel for escape of the gas is the lymphatics. In many communications on this subject (Turnure, Eisenlohr, Urban, Moore—cases 1 and 2) the distention of the lymphatics and lymph nodes with gas has been a prominent feature of the case. Although the cisterna chyli has been reported as distended with gas by several authors who have had this point in mind during autopsy, I have been unable to find reports of cases which would suggest that air embolism occurs.

If the gas becomes solidly walled off and encapsulated by fibrous tissues, resorption is extremely slow.

CLINICAL DIAGNOSIS

Thus far the clinical diagnosis has not been made, although the diagnosis has been confirmed by proctoscopy after it had been predicted roentgenologically.[12d] The possibility of intestinal emphysema should be borne in mind when dealing with pyloric obstruction or any chronic disease of the small or large bowel. Unexplained pneumoperitoneum should be viewed with suspicion. Precise diagnosis, however, would probably involve demonstration of gas cysts in the vagina or rectum. Palpatory findings have not in the past led to a correct diagnosis, and the crepitation which might be expected has not been elicited. Perhaps the most suggestive finding would be a history of vomiting, bloody diarrhea and jaundice in an infant. Such findings should always be checked by the simple expedient of requesting a scout film of the abdomen.

ROENTGENOLOGIC DIAGNOSIS

The roentgen findings are as protean as the manifestations of the disease itself. At least six partially overlapping syndromes can be outlined.

1. The typical reticular appearance of the abdomen produced by cystic accumulation of gas described by Gazin, Forfota, Ruckstein er and Kux, Turnure and others.

2. The highly characteristic double ring shadow or inflated sausage appearance noted in the two cases reported here.

3. Unexplained pneumoperitoneum. With this finding the abdomen should be carefully searched for other signs of pneumatosis as listed under headings 1 and 2. Conditions to be differentiated, however, are recent surgery and in females the performance of the Rubin test, indulgence in knee-chest exercises, intercourse or forceful douches.

4. Unusual accumulation of air in the vagina, retroperitoneal tissues, perirenal area, bladder and so on.

5. Separation of the liver from the right leaf of the diaphragm. This may be the result of interposition of a loop of intestine, but the cytsic appearance of gas in large emphysematous cysts may mimic the pattern of distended small bowel. Several cases reported under this heading probably represent gas in the triangular ligament of the liver.

6. Atypical ulcerative colitis. Urban has noted the possibility of making a diagnosis of pneumatosis in cases of ulcerative colitis in which there is sudden remission of the roentgen signs with restoration of the ragged pattern of the colonic mucosa to normal in a few weeks.

SUMMARY

Two cases of preoperatively diagnosed pneumatosis intestinalis in the newborn are presented. A new roentgen sign of this condition is reported. The protean manifestations of interstitial gas are collected, and a unified theory which gives a reasonable account of its genesis is introduced.

The roentgen signs which may lead to diagnosis of pneumatosis intestinalis are discussed.

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Dr. Cameron Haight performed the operations, and Drs. J. L. Wilson, Fred J. Hodges and John F. Holt gave permission to publish these cases.

CORRELATION OF EPILEPTIC SEIZURES, ELECTROENCEPHALOGRAMS AND EMOTIONAL STATE

Some Preliminary Observations in Several Children

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AND
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IT IS OUR purpose in this brief paper to record some observations on the correlation of the frequency and intensity of epileptic seizures, the degree of abnormality of the electroencephalograms and the emotional state in several children. These correlations have become evident both to the psychiatrist (I. N. B.) and the electroencephalographer (C. L. Y.) independently and have resulted in the present collaboration.

If one were to arrange diseases in a scale ranging from those that are primarily impersonal disease processes, such as cancer, to those in which the interpersonal, emotional factors play a large part in the somatic manifestations of the disease, such as peptic ulcer, one would find great disagreement about where one could place epilepsy. Although all workers acknowledge the fact that strong emotion may act to precipitate convulsions, most investigators of epilepsy agree with Lennox,[1] who states that epilepsy is a problem entirely of disordered neurophysiology and not psychology and, therefore, the understanding, as well as the treatment, of epilepsy is not to be found in psychopathology and psychotherapy, but in pathophysiology and antiepileptic medication. Recently a number of workers have been impressed with the interpersonal factors which seem to be significant in many epileptics. Thus, Aring, Rosenbaum and Lederer [2] feel that the epileptic seizure may be a defense against anxiety and suggest that the convulsion may be a form of discharging emotions. They are of the opinion that, as in migraine, psychotherapy may be an effective adjunct in treatment of the disorder. Schick [3] and Liss [4] also stress the

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1. Lennox, W. G.: Psychiatry, Psychology, and Seizures, Am. J. Orthopsychiat. **19**:432, 1949.

2. Aring, C. D.; Lederer, H. D., and Rosenbaum, M.: The Role of Emotion in the Causation of Epilepsy, A. Res. Nerv. & Ment. Dis., Proc. **26**:561, 1947; personal communication to the authors of a paper read before the meeting of the International League Against Epilepsy, Cincinnati, April 16, 1950.

3. Schick, A.: A Contribution to the Psychopathology of Genuine Epilepsy, Psychoanalyt. Rev. **36**:217, 1949.

4. Liss, E.: Art Work of an Epileptic Child, Psychosom. Med. **11**:315, 1949.

effectiveness of psychotherapy in draining of emotions, especially aggression, hostility and anxiety, that might otherwise be expressed via the seizure. They feel that psychotherapy may result in a decrease in number and severity of the fits and permit the use of smaller doses of anticonvulsant medicaments to control the disorder.

As far as epilepsy in children is concerned, there seems to be general agreement that the emotional state of the child may affect the severity and frequency of seizures. Bridge [5] in his recent book documents his own observations and refers to the general experience recorded in the literature to bear this out. Bridge expresses the view that by educating the parents about the disease and treating the child's emotional problems the epileptic seizures either markedly decrease in frequency or often completely cease. In some instances it has been possible to discontinue anticonvulsant medication with no recrudescence of seizures. Liss has noted that an unstable family situation often greatly aggravates the incidence and severity of seizures and that psychotherapy of the child may help reduce frequency and gravity of the fits.

Recent thought of workers at some psychiatric centers for children, and particularly at this one,[6] considers the emotional disturbance of the child as symptomatic of emotional disturbances and conflict in the setting from which the child comes. The psychopathological involvement of the child is seen as the outcome of his relationships with one or more significant adults who are themselves disturbed, although often not manifestly so. Thus, the child's problems are seen as family problems. Not only do the parents' conflicts influence the child, but the child's difficulties, in turn, affect the parents, resulting in an interminable circular process. Thus, in addition to work with the child, treatment for the parents seems indicated. Sperling [7] has recently strongly advocated psychotherapy for mothers of children with psychosomatic diseases in order to treat effectively the disorder of the child.

PRESENT STUDY

One of us (I. N. B.), in the course of psychotherapeutic work with several adult patients who were epileptic, observed with interest the apparent correlation between the state of emotional tension in the patient and the number and severity of minor or major seizures reported. It seemed that, with effective therapy and reduction of tension, there was often also a reduction in the number and severity of seizures, and in two instances it was possible to reduce markedly the amount of antiepileptic medication necessary to control the seizures. Subsequent observations in a children's ward further stimulated interest in the manner in which the petit mal and grand mal seizures in the children seemed to be correlated with the state of the child's feelings. Since we feel strongly that the interaction between the parent and child and the reciprocal effect of one on the other must be understood and dealt with in the collaborative therapeutic effort, we wondered whether it might be possible to observe the manner in which variations in tension during therapeutic work with the parents would affect the seizures of the child.

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5. Bridge, E. M.: Epilepsy and Convulsive Disorders in Children, New York, McGraw-Hill Book Company, Inc., 1949.

6. Szurek, S. A.: An Attitude Towards Child Psychiatry, Quart. J. Child Behavior **1**:22, 178, 375 and 401, 1949.

7. Sperling, M.: The Handling of Mothers of Children with Psychosomatic Disorders, Psychosom. Med. **11**:315, 1949.

Since each of us had independently noted some correlation of the emotional state of the child, the number of seizures and the electroencephalographic picture, we decided to investigate these features. We chose cases in which neither of us was involved and attempted in each case to correlate the observations in the therapists' notes concerning the emotional status of the parents and the child, the number and intensity of seizures reported in the nurses' records or by the parents and the electroencephalograms which were taken either regularly or, as in some instances, haphazardly before this correlation was begun. We here present our preliminary observations in short histories and illustrative electroencephalographic records for four cases. We do this with full awareness of the shortcomings of the retrospective analyses of therapists' notes, as well as the fact that single electroencephalograms reveal only the momentary electrical state of the brain and can be indicative only of the patient's general status. However, we feel that the summation and correlation of all the data, both empirical and subjective, no matter how fragmentary, may be of value.

Treatment of these families has been carried on for varying periods and with varying effectiveness, to some extent determined by the continuity of therapists and the skill and training of the therapists involved. Several of the cases herein presented will at some later date be made the subject of individual papers by the therapists concerned. Here we are concerned only with some of the over-all observations and not the details of treatment.

REPORT OF CASES

CASE 1.—Sammy, aged 4½ years, and his parents have been receiving treatment for 10 months. His seizures began at 9 months of age with an encephalitis of unknown origin. This is reported to have been characterized by severe stupor, prolonged convulsions and increased spinal fluid pressure to 600 mm. of water. At the age of 2 years he had his first petit mal seizure. For several months prior to this, he was very aggressive, had severe temper tantrums and banged his head a great deal. Subsequently, he had almost daily petit mal seizures. At the birth of a baby sister, when Sammy was 2 years 9 months of age, his temper tantrums increased; he became quite destructive and aggressive toward the baby sister. Simultaneously, his minor seizures increased in frequency. It was reported that he had four or five petit mal seizures daily. Medication with phenobarbital, trimethadione (tridione®) and mephobarbital (mebaral®) successively resulted in only transient improvement. Just prior to hospitalization, all medication was stopped and he continued to have three or more minor attacks daily. Also at this time the question of mental deficiency was raised by psychologists who saw the child. Sammy was accepted for hospitalization in order to determine the degree of organic involvement and to help the parents with the severe conflicts within themselves and between them, so that they could better plan their own future and that of the child. While in the ward, Sammy at first was well behaved. As the parents' initial relief at having the child out of the home wore off, their tensions became evident, as did the conflicts between them. Sammy's behavior became more aggressive and demanding in the ward. He had only rare minor seizures in the hospital, but frequent petit mal episodes occurred on visits home. Electroencephalograms taken with the child under sedation shortly after entry revealed a moderate petit mal tracing, with bursts of 3 per second, high amplitude spike and dome waves. When the parents left the state on a prolonged business trip, Sammy's petit mal seizures in the ward became more frequent—two or three daily. His first grand mal seizure occurred during a visit home, when he was being thwarted in the acquisition of a toy. Subsequently, major seizures began to appear while he was in the ward. Work with the parents was extremly slow, and the boy's behavior remained very difficult to manage until the last few months, during which there have been periods of relative peace between the parents that has been reflected in Sammy's quieter, less disturbed behavior in the ward. About this time, administration of phenobarbital, 1 grain (0.06 Gm.)

daily, was started and, in contrast to previous reports, this controlled all seizures. In the last month, work with the parents has seemed more encouraging, and Sammy has been somewhat easier. The last electroencephalogram, also done with the child under sedation, two months ago, showed a severely disordered record, with asynchrony between the temporal areas and bursts of 3 per second, high amplitude, irregular topped waves with numerous spikes. We hope that continued work with Sammy and his parents will result in enough improvement in Sammy's behavior to assure better cooperation in further electroencephalographic studies. We would predict some improvement in the record at present. We hope to report on this case more fully at a later date.

Case 2.—Peter, aged 3½ years, and his mother have been receiving treatment for seven months. Peter's initial seizures began with several generalized convulsions at 3 to 4 months of age. There was no recurrence until 14 months of age, at which time he had a febrile illness and a convulsion lasting several hours that required hospitalization. The third convulsive episode occurred at 38 months of age and was characterized by an outcry, cyanosis and unconsciousness, lasting three to five minutes. Peter's mother stated that the child has had jaundice with every mild respiratory infection he has had since 6 or 7 months of age. A mild hepatitis was diagnosed after extensive study during a previous hospitalization. At 39 months of age Peter had a tonsillectomy and on return from the hospital began to have five to eight "spells" each night while asleep, and several during his afternoon naps. These "spells" consisted of a loud grunt, some thrashing movements of the entire body and slight cyanosis and were 30 to 60 seconds in duration. According to reports, Peter awakened from the spells somewhat dazed

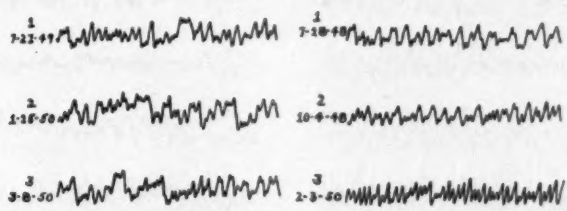

Fig. 1.—Left, in case 1 electroencephalogram became worse during period of hospitalization (13 months). During this period there was evidence of increased tension in the parents. Right, in case 4 the electroencephalographic improvement in tracing 3 coincides with beginning of reduction of tension in girl and mother.

and asked, "Do you love me, Mommy?" and then went back to sleep. Early in therapy, the mother seemed to be quite defensive and hostile and did not appear to trust anyone. Initially, Peter had occasional seizures while in the ward but was reported to have the usual number on visits home. During prolonged stays in the hospital he had few seizures, but on his return from visits home Peter seemed tense and anxious and had an increased number of seizures. His electroencephalogram originally showed a marked diffuse paroxysmal dysrhythmia, with several observed seizures of petit mal during the recording, and some out of phase activity in the temporal regions. To date 24 electroencephalograms have been taken, and at the beginning the records made the day after Peter's return from visits home were more abnormal than those taken during periods of continued residence in the ward.

As the mother began to discuss her ambivalent feelings about keeping the child, she became very hostile to members of the staff. She was alternately submissive and ingratiating or very demanding and strict with the boy. During this period, Peter had numerous seizures in his sleep and his electroencephalograms became worse. As the mother found her therapist accepted her no matter what feelings she expressed, she became noticeably easier. The treatment with phenobarbital, which from the onset of medication had not been very effective, now seemed to control the child's seizures, so that they became quite rare. His electroencephalograms during that period improved, though they have never become completely normal. Then, as the mother was faced with the departure of her therapist to another service, she again became quite tense and disturbed and seemed unable to manage Peter and unwilling to have him home for visits. Peter then had an exacerbation of seizures, and for the first time some unilateral

clonic movements were noted. The amount of medication was subsequently increased, with some improvement. The electroencephalograms during this period were much worse, and there were "brief equivalent attacks noted, and later some grand mal fast activity was seen."

As the mother was helped to express her anxieties about the therapist's leaving, she again became fairly relaxed. She has been able to take Peter out of the hospital and to keep him at home. Peter has had no further seizures with administration of 2 grains (0.13 Gm.) of phenobarbital daily. The mother and Peter continue to be seen for therapy as outpatients. Recent electroencephalograms indicate a trend toward improvement of the dysrhythmia, except

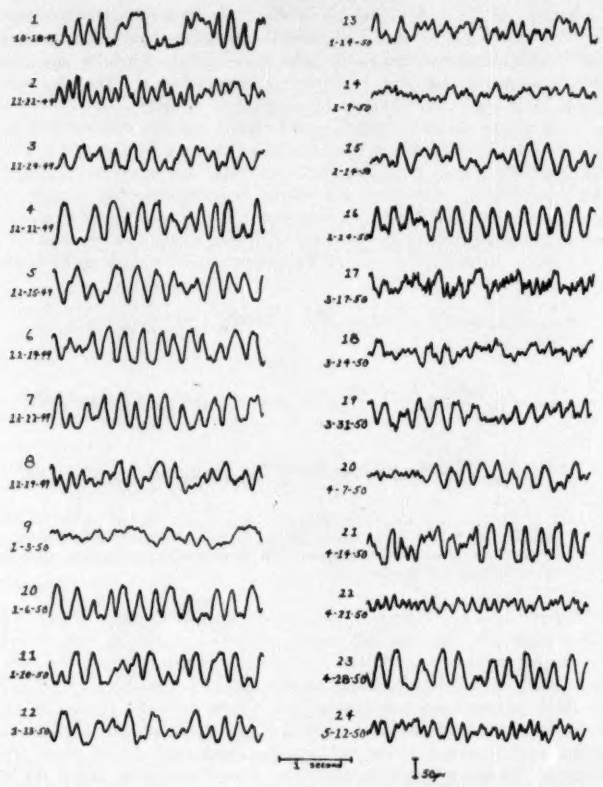

Fig. 2.—*1*, initial electroencephalogram in case 2 shows severe dysrhythmia and slow activity. *2*, noticeable improvement after three weeks' hospitalization. *3* to *7*, electroencephalogram worse again with period of increased tension in mother. *8*, electroencephalogram improved; mother less tense. *9*, electroencephalogram immediately following convulsion; child was drowsy. *10* to *14*, electroencephalograms progressively improved. Mother more at ease. *15* to *17*, electroencephalograms show exacerbation of severe dysrhythmia. *17* shows fast grand mal type waves; increased tension at time of departure of therapist. *18* to *21*, after electroencephalogram improved (*18*), it again became worse during period of mother's first acquaintance with new therapist. *22* and *24*, electroencephalogram noticeably improved; tension minimal. *23*, electroencephalogram shows exacerbation at time of father's accident and hospitalization, which also coincided with moribund condition of grandfather. *24* was taken after both father and grandfather's conditions improved.

for a severer dysrhythmia noted at the time the father had been in a serious accident and the grandfather was hospitalized and was seemingly moribund. At that time, the mother was quite

tense, as was the child. The next week, both the father and the grandfather were out of danger, the mother and Peter were easier and the electroencephalogram was again much improved. There were no seizures reported during this period.

CASE 3.—Sally, aged 7½ years, her mother and grandmother have been receiving therapy at this clinic for 2½ years. Sally's first seizures were noted at 8 months of age and were petit mal in type. The mother had had a difficult pregnancy with pernicious vomiting and a prolonged labor of over 30 hours which was ended by midforceps delivery. Despite the onset of petit mal seizures at 8 months, they remained as occasional attacks until the age of 2 and then became more frequent. When Sally was 3 years old, a brother was born and the parents separated. Shortly thereafter, Sally began to have grand mal seizures of such severity and frequency as to require hospitalization. A pneumoencephalogram done at that time was normal. Psychological tests revealed an intelligence quotient of 100. Diphenylhydantoin (dilantin®) sodium and phenobarbital medication did not seem to alter the seizure rate or severity for the next several years. At the age of 5, her intelligence quotient could not be obtained validly because of her lethargic, apathetic behavior, and she appeared mentally retarded. Sally was admitted to the children's ward in order to evaluate the organic and emotional components of the disorder and to help the mother with her problems with respect to this child. It soon became evident that the grandmother was also involved in the total situation, and she insisted on being included in treatment.

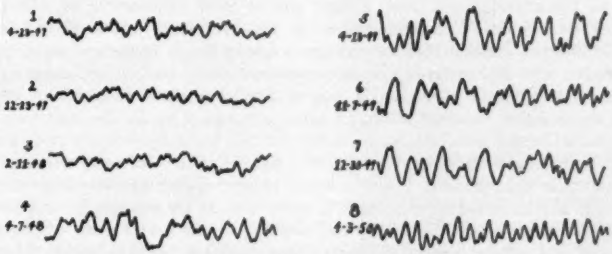

Fig. 3.—Electroencephalograms in case 3. *1*, prehospitalization slow activity and mild to moderate paroxysmal dysrhythmia. *2* and *3*, improvement during period of relative ease in mother early in hospitalization of child. *4* and *5*, increased dysrhythmia correlated with periods of increased tension in therapy of mother and grandmother. *6* and *7*, discontinuance of medication and period of increased tension between mother and grandmother. *8*, electroencephalogram nearly normal. Patient was being treated with phenacetylurea, and tendencies toward resolution in intrafamilial conflicts were present.

On admission Sally appeared lethargic and dull, as though drugged, although she had been without medication for several months. In the past several years members of the staff have come to recognize this look as symptomatic of increased tension in the mother and to realize that it may often precede the onset of seizures. The initial electroencephalogram revealed high amplitude, irregular, slow waves in all leads, with occasional bursts of spike and dome activity in all leads and several spindles of 30 cycle per second high voltage waves scattered throughout the record.

Two and a half years' work with this family has resulted in many swings in therapy as particular problems were being worked through. At impasses in the work the anxiety and tension in both the mother and the grandmother, but primarily in the mother, were reflected in the withdrawal and somnolent behavior of Sally, with an increased number of seizures, regardless of the nature of the medicament being given or its dosage. Thus, eight months after entry when things were going along quite smoothly, the electroencephalogram revealed a record considered normal for a 5 year old child. When a crisis developed, as on one occasion in mid-1948, a generalized dysrhythmia was seen in the tracing and frequent fits were noted while the child was in the ward. An attempt to discontinue medication at a time that the child's therapist felt his ties with Sally might effectively prevent seizures coincided with a fairly difficult period in the mother's and grandmother's treatment. There were frequent grand mal seizures which required

reinstitution of medication. An electroencephalogram taken at this time revealed a severe paroxysmal dysrhythmia of high amplitude spikes and slow waves and larval grand mal bursts. This was the worst record seen.

Subsequently, therapy with the adult members of the family has been more effective, and Sally has appeared brighter, more alert and more a part of the ward community. At this time treatment was started with 250 mg. of phenacetylurea given four times a day, and she has had no further seizures. Her electroencephalograms have become progressively less disturbed, and a recent one revealed a well established 7 to 8 cycle per second tracing, with some random 4 cycle per second waves and no evidence of paroxysmal bursts of fast or spike and dome waves. Resolution of some of the intrafamilial problems seems to have enabled the mother to make plans to have Sally at home with her.

Case 4.—Rose, an 18 year old adolescent girl, and her mother have been receiving treatment for almost two years. At the age of 13 Rose had what was thought to be acute encephalitis, with severe convulsions, stupor and a residual paralysis of the left arm. Throughout the onset of the illness and during its course hysterical aspects were noted, and these continue to be prominent. Rose's previous medical history was essentially noncontributory, except for a recurring atopic dermatitis since the age of 3 years. After hospitalization, Rose had four or five grand mal seizures daily, with focal signs on the left and incontinence. Her left arm and hand continued to be paralyzed, though it was often felt this was hysterical, especially since on examination the sensory changes rarely followed anatomic lines. For almost two years psychoanalytic therapy four times weekly was tried, without alleviation of frequency or severity of seizures. The mother became Rose's constant companion, and everything was sacrificed for her. An electroencephalogram early in 1948 showed severe dysrhythmia. There was slight improvement in the seizures with diphenylhydantoin administration. Both mother and daughter presented themselves for help at our clinic late in August 1948. For many months with inexperienced therapists the situation remained about the same, although Rose for the first time associated with boys and adolescent girls. Gradually, as one therapist began to work with both Rose and her mother and both became less tense, their conflicts came more into the open, and some tendencies toward resolution were evident. Rose's seizures became fewer; her atopic dermatitis, which flared up with any increased tension, began to abate, and, as the therapist became progressively more effective in dealing with the mother and daughter, the amount of anticonvulsant medication was decreased and seizures became fairly rare—one every two or three weeks. Rose started to school and began to enjoy the activities of her group. She became very much interested in drama and took part in school plays. The electroencephalograms at the onset of treatment showed paroxysmal dysrhythmia of high amplitude, irregularly flat-topped waves with a mild to moderate right temporal focus persistent throughout the record. The most recent electroencephalogram is an essentially normal record.

SUMMARY AND CONCLUSIONS

We present four brief case histories which illustrate some observations on the effect of the feelings of the child's parents on the child's emotional state and thus on the frequency and severity of epileptic seizures, as well as on the abnormality of the electroencephalograms.

From our preliminary observations we feel a direct correlation may exist. We would at this time be willing to state that psychotherapy with both child and parents may prove to be an important factor in the treatment of epilepsy in the child in whom psychological conflicts exist in addition to the epilepsy.

We hope to implement these observations further and to present them at a later date in greater detail.

Case Reports

PSEUDO TRILOCULAR BIATRIAL HEART WITHOUT PULMONARY STENOSIS

Report of a Case and Discussion of the Related Embryology

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AND
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BECAUSE of continued improvement in the efficiency of the surgical approach to the treatment of congenital heart disease, it has become increasingly important to recognize the various types of congenital heart disease. Understanding can be advanced and more adequate methods for the treatment of congenital cardiac abnormalities can be developed only through the observation of variations of the already familiar basic patterns of congenital heart disease. Thus, we consider it worth while to describe a case of an anomalous cardiac condition showing additional minor valvular developmental abnormalities which combine to produce a situation not previously reported in the literature.

REPORT OF CASE

Clinical Brief.—R. F., a white male infant, was hospitalized on four different occasions in the pediatric department of the North Carolina Baptist Hospital. He was seen first in September 1947 at the age of 6 months. The infant was said to have been normal until the age of 3 months, when his lips were seen to become blue during prolonged crying. The cyanosis persisted and increased in intensity. At 5 months of age the cyanotic attacks became associated with marked dyspnea. Maternal history was negative for infectious diseases during pregnancy.

Physical examination revealed an apparently well developed and well nourished infant with deep and rapid respiration. The lips and nail beds showed moderate cyanosis. There was a thrill over the third left interspace near the sternal border. The left cardiac border was found by percussion to be 3 cm. outside the left nipple line. The right cardiac border was found to be 3 cm. to the right of the sternum by percussion. A loud, rough, grade III systolic murmur was heard over the entire precordium, loudest over the left third interspace near the sternum. This murmur was transmitted to the left side of the neck and to the left axilla and back. The liver edge was firm, nontender and palpable 3 cm. below the right costal margin. The urine and blood studies showed no abnormal results. Chest fluoroscopy was interpreted as showing right ventricular hypertrophy with decrease in prominence of the pulmonary artery. An electrocardiogram showed slurring of the QRS complex in lead I, deep S wave in leads III and IV with elevation of the ST segment in leads II, III and IV and left axis deviation. The patient was treated symptomatically and was discharged in two weeks.

At 7½ months of age the infant was readmitted, having had several convulsions accompanied with deep cyanosis. The seizures were characterized by rigidity, tonic and clonic contractions of the extremities and retraction of the neck, followed by generalized flaccidity. Except for slight clubbing of the fingers and toes, the physical examination showed the same results as did the examination at the previous admission. Treatment during the second admission was symptomatic, and the patient was discharged in five days without further studies being done.

At 11½ months of age he was hospitalized because of pneumonia. During this admission, he became deeply cyanotic and edema of the face, hands and abdomen developed. It became

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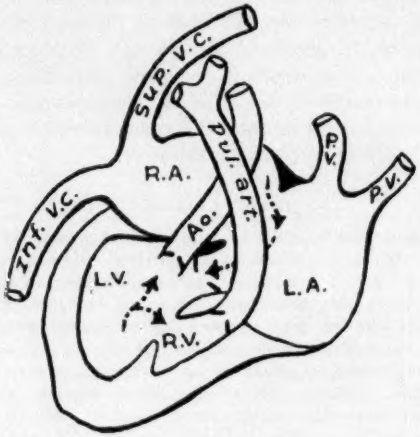
necessary to treat him with oxygen and digitalis, the latter failing to produce any appreciable immediate improvement in his cardiac status. The pneumonia responded to penicillin treatment, and evidence of cardiac failure disappeared. He was not cyanotic on the thirteenth day of hospitalization.

The fourth and final admission was in September 1948 at the age of 17½ months. During the five month interim between the third and fourth admissions, convulsive episodes continued, becoming more frequent and prolonged. These attacks consisted of stiffening of the body, vomiting, breath holding and rolling of the eyes. During these attacks he would become markedly cyanotic. Physical findings on this admission were similar to those noted previously. The cyanosis and clubbing were more marked, and the systolic heart murmur had acquired a whistling quality. Blood studies revealed polycythemia. The results of electrocardiographic studies and chest fluoroscopy were essentially unchanged. Though there was considerable difference of opinion, a combination of pulmonary stenosis and tricuspid atresia was thought to be the most likely diagnostic possibility. On the eighth hospital day an anastomosis was created between the aorta and the pulmonary artery. During and after the procedure the infant was markedly cyanotic. Two hours postoperatively, gasping respirations developed and he died.



Pesudo trilocular biatrial heart without pulmonary stenosis; *Inf. V.C.* indicates inferior vena cava; *Sup. V.C.*, superior vena cava; *Pul. art.*, pulmonary artery; *P.V.*, pulmonary vein; *Ao.*, aorta; *R.A.*, right atrium; *L.A.*, left atrium; *R.V.*, right ventricle; *L.V.*, left ventricle.

Necropsy.—The body of this well developed and well nourished white boy weighed 12,700 Gm. and was 53 cm. long (normal for this age, 12,000 Gm. and 83 cm.), and there was deep cyanosis of the lips and mucous membranes. There were no edema or ascites. There were no external anomalies. A moderate left hemothorax and hydropericardium were present. The right lung was hyperemic and edematous. The left lung was atelectatic. The liver was not congested. The heart was enlarged, abnormally shaped and weighed 75 Gm. (normal for this age, 55 Gm.). The heart was rotated anteriorly and to the right, so that the apex lay in the right anterior oblique plane of the thoracic cavity. The atria were rotated to the right, so that the right atrium was to the left of the sternum and the left atrium was posterior and to the right. There were no venous anomalies. A probe introduced into the heart through the pulmonary artery passed into the right ventricle; another introduced into the aorta passed into the left ventricle.

The right and left atrial chambers were markedly dilated and were partially separated by a thin endocardial septum which was entirely absent posteriorly. There was no right atrioventricular orifice. There was an intact, delicate endocardial septum, measuring 4.0 mm. in diameter, occupying the position in which the tricuspid valve is normally situated.

The left ventricle was markedly dilated and its musculature uniformly thickened. The right ventricle was represented by a small chamber with a capacity of approximately 3.0 cc. The two ventricles were separated by an interventricular septum which had an oval defect measuring 1.0 cm. in diameter.

The left atrioventricular valve was tricuspid but otherwise normal. The pulmonary artery was not stenosed. The aortic valve presented no abnormalities, and the aorta was left sided. The ductus arteriosus was fibrotic, and its lumen obliterated. The surgical anastomosis between the aorta and the pulmonary artery was located 1.0 cm. distal to the ligamentum arteriosum and presented a satisfactory lumen measuring 2.0 mm. in diameter. There were no other significant gross findings.

Histologically, sections of tissues, stained with hematoxylin and eosin, revealed myocardial hypertrophy, slight interstitial myocardial fibrosis and pulmonary congestion with marked atelectasis.

COMMENT

The basic type of congenital anomaly in the case presented here has been previously reported by Peacock,[1] Abbott [2] and Taussig.[3] Fundamentally it represents a pseudo trilocular biatrial heart. All previously reported cases have presented pulmonary infundibular stenosis. They have not presented the dextrocardia and the combination of valvular abnormalities noted in the necropsy specimen in this case.

Because embryologists are not agreed as to the method of fusion of the four heart chambers, an exact explanation of the mechanism of the anomalous development in all instances is not possible. However, the ideas in general are similar, and relatively satisfactory explanations may be advanced.[4]

Between the fifth and sixth week of embryonic life the cardiac tube grows faster than the pericardial cavity in which it lies, and as a result the heart is compelled to bend.[5] The growth tendencies are such that the chief early flexure is to the right, throwing the ventricular loop farther caudad and ventrad. At the same time the atrium and the sinus venosus assume a dorsal and cephalic position, accomplishing by rotation an essential reversal of the original relations of the primitive parts of the heart. In dextrocardia the primitive cardiac loop swings in the reverse of the normal direction, and the apex points to the right. The position of the heart in the thoracic cavity is not one of a front to back rotation but is a mirror image of the normal cardiac position. Dextrocardia is usually associated with general inversion of the viscera. When situs inversus is absent, dextrocardia is usually associated with grave congenital cardiac abnormalities.

The presence of an atrial septal defect results from improper fusion of the septum primum and septum secundum. The end of the sixth fetal week marks the appearance of the septum secundum just to the right of the already present septum primum. Failure of development of the septum secundum is responsible for the presence of a large atrial septal defect posteriorly.

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1. Peacock, T. B.; Cor Triloculare Biatriatum with Anomalous Septum Cutting off Rudimentary Right Chamber, Tr. Path. Soc. London. **6**:117, 1855.

2. Abbott, M. E.: Atlas of Congenital Cardiac Disease, New York, The American Heart Association, 1936.

3. Taussig, H. B.: Congenital Malformations of the Heart, New York, Commonwealth Fund, 1947.

4. Jordan, H. E., and Kindred, J. E.: A Textbook of Embryology, New York, Century Company, 1926. Abbott.[2] Taussig.[3]

5. Arey, L. B.: Developmental Anatomy: A Textbook and Laboratory Manual of Embryology, ed. 4, Philadelphia, W. B. Saunders Company, 1942.

In the primitive single ventricular cavity there appears a median elevation which extends to the ventral endocardial cushion. Early in the eighth week of fetal life the ventricles become completely separated by the septum membranaceum, which is formed by the union of the median ventricular ridge, the proximal bulbar septum and the fused portion of the endocardial cushions. Failure of formation of the septum membranaceum results in a patent interventricular septum.

Valvular abnormalities may occur in both semilunar and atrioventricular valves. Such variations may involve either the size or the number of cusps. The latter condition is caused by an atypical division of the bulbus or from irregularities in the arrangement, division or fusion of the padlike primordia about the primitive atrioventricular canal. The primordia of the pulmonary valves are prominent in embryos of 6 or 7 weeks.

A rudimentary right ventricle cannot be explained as readily as most of the other defects. It is felt, however, that it is a phenomenon which results directly from a relative disuse of the right ventricle secondary to tricuspid atresia. The interventricular septum is brought into existence by the enlargement of the future halves of the ventricle on its two sides. The septum increases in height proportionately as the ventricular sacs grow deeper. It logically follows that there would be little physiologic stimulus for the right ventricle to enlarge further, since only small amounts of blood are able to gain access to it through the septal defect. However, it does not seem logical that a relatively normal pulmonary artery would arise from such an underdeveloped chamber.

The diagnosis of cor biatriatum triloculare should not be extremely difficult. Although the physical findings present in certain cases of tetralogy of Fallot are often quite similar to those presented by cor biatriatum triloculare, there are obvious differences in laboratory findings. In tetralogy, fluoroscopy shows a strikingly small heart, no left ventricular enlargement, moderate or marked right ventricular enlargement and frequently a right aortic arch. The electrocardiogram always shows marked right axis deviation. In tricuspid atresia and underdevelopment of the right ventricle, fluoroscopy shows cardiac enlargement and absence of a right ventricular shadow. The electrocardiogram usually shows a left axis deviation. According to Taussig,[3] occasionally very young infants suffering from this cardiac anomaly will have a balanced electrocardiogram, in contrast to the right axis deviation normally seen during the neonatal period.

The surgical treatment of this fortunately rare type of congenital heart disease is not very satisfactory at the present time. The condition is seldom compatible with more than a few years of life, though we have seen one patient who died after a surgical procedure at the age of 35 years who was found at autopsy to have cor biatriatum triloculare. Some relief may be obtained by the creation of a functional ductus in those cases in which the ductus arteriosus is not patent. It is most interesting to speculate in regard to the improvement which may be afforded by tricuspid valotomy as this procedure is further perfected.

SUMMARY

A case of congenital heart disease of the pseudotrilocular biatrial type is presented. Brief embryologic explanations are offered for dextrocardia, atrial septal defects, ventricular septal defects, valvular abnormalities and underdevelopment of the right ventricle. Comments are made relative to the diagnosis and surgical treatment of cor biatriatum triloculare.

HEMANGIOMA WITH PURPURA, THROMBOCYTOPENIA AND ERYTHROCYTOPENIA

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CASES OF hemangiomas associated with blood dyscrasias are so rare that insufficient data have been accumulated either to determine the true significance of the association of these conditions or to evaluate properly the efficiency of modern methods of treatment.

HISTORY

Hemangioma associated with purpura has been reported in three cases. Kasabach and Merritt [1] reported a case of a 2 month old infant in whom the thrombocyte (platelet) count was reduced and the purpura spread. The infant was treated with roentgen irradiation and later with radium needles with subsequent recovery.

The second case was reported by Rhodes and Borrelli [2] of an infant 3½ months of age. A mass, supposedly lipomatous at birth, became larger and bluish, and petechiae appeared over the body; the thrombocyte count was low. This patient was treated with transfusions, a vitamin K preparation and larger doses of roentgen irradiation, with ultimate recovery.

The third case was reported by Silver and his associates.[3] This child was treated as early as 3½ months of age with solid carbon dioxide and at 5 months, and again at 11 months, with roentgen irradiation. At 18 months the picture became progressively worse and ended fatally.

The case presently reported was first diagnosed in a boy at the age of 6 weeks. He was treated by transfusions, roentgen irradiation and splenectomy, resulting in ultimate recovery. Of striking interest was the blood picture, which was that of thrombocytopenia and erythrocytopenia.

REPORT OF A CASE

F. S., a 6 week old boy, was admitted to the hospital on Sept. 6, 1947, with a history of progressive enlargement of a discolored mass on the right wall of the chest. The mother stated that the mass had been present since the patient's birth and had been approximately the size of a tennis ball with no increase in size until the present illness. She had been informed by a physician that the lesion was a hemangioma, and future local treatment was anticipated.

Dr. Bogin is from the Department of Pediatrics and Dr. Thurmond from the Department of Surgery, Bridgeport Hospital.

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On the morning of September 5, when the infant was taken from his crib by the mother, there was noted a large area of bluish discoloration about the original lesion with extension anteriorly around the wall of the chest as far as the right nipple. The mother was certain that none of the discoloration was present on the previous night, and there was no history of trauma. The discoloration advanced slowly during that day and the next night, and on the following morning the infant was brought to the hospital.

There was no history of previous abnormal bleeding. Circumcision had been performed four days after birth without significant bleeding.

The general health of the patient had been excellent, and growth and development were normal.

The mother's pregnancy, which was her first, had been normal. The mother gave a history of a tendency to bruise easily, but there was no antepartum bleeding and no overt hemorrhage during or after parturition. Subsequent blood studies showed normal erythrocyte, leukocyte and thrombocyte counts and normal bleeding and clotting times.

Results of Physical Examination.—The patient was a robust 6 week old infant with massive discoloration of the right wall of the chest. Examination of the eyes, ears, nose and throat revealed no abnormalities. There was no evidence of petechial hemorrhages into the conjunctiva. The heart and lungs were normal. Located at the right posterior axillary fold was a bluish red mass about the size of an orange with surrounding subcutaneous ecchymosis extending superiorly to the clavicle, anteriorly to the sternum, inferiorly to the iliac crest

Fig. 1.—Photograph showing extent of hemangioma and purpura.

and posteriorly to the midline. The tissues were tense, particularly those overlying the site of the primary hemangioma. The spleen was not palpable.

Laboratory Studies on Admission.—Red blood cells numbered 2,270,000 per cubic millimeter. The hemoglobin concentration was 9.55 Gm. There were 11,200 white blood cells, with a normal differential count. Bleeding time was 11 minutes 29 seconds. Capillary coagulation time was 5 minutes 30 seconds. Blood thrombocytes numbered 22,700 per cubic millimeter. Urinalysis gave normal results.

The clinical impression on admission was hemangioma of the right anterior wall of the chest with spontaneous hemorrhage due to a blood dyscrasia, probably thrombocytopenic purpura. Conservative treatment consisting of repeated small whole blood transfusions and intramuscular administration of a vitamin K analog was instituted. The first transfusion of 80 cc. of whole blood was given on the night of the first hospital day, and one of like amount was given daily for the next three days. The erythrocyte count rose to 4,100,000 per cubic millimeter, the patient's general condition was better and there was less evidence of active bleeding.

The infant did well for six days without transfusions but on September 15 began to bleed into the tissues of the wall of the chest again, even more profusely than on the first occasion. The bleeding time was recorded as 15 minutes "+," as it was necessary to stop the bleeding by firm and prolonged pressure after that length of time. The tourniquet test had a markedly positive reaction, and there was bleeding from a blood count puncture site for two hours. The thrombocytes dropped to 5,600 per cubic millimeter. The bleeding continued despite administration of daily blood transfusions, a vitamin K preparation and thromboplastin subcutaneously (fig. 1).

The next conservative measures employed were irradiation of the spleen and local radium application to the hemangioma. On September 17 and 18 the patient received 50 r of roentgen irradiation to the anterior and posterior splenic areas, but no significant response was obtained. On September 18 a tray with 300 mg. of radium was applied to the primary hemangioma for one hour.

During the next few days there was no additional bleeding, but on September 24 the thrombocyte and red blood cell counts and hemoglobin concentration dropped sharply, and another transfusion of whole blood was given. At this time, it was felt that the infant had hypersplenism causing thrombocytopenia and anemia and splenectomy might be necessary as a last resort.

From September 29 to October 4 the patient received roentgen irradiation in a dosage of 50 r daily to the anterior or posterior splenic areas, but no definite response could be demonstrated, so the treatment was discontinued. On October 4 the patient's general condition was good. The bleeding time was still varying from 5 to 10 minutes, and the thrombocytes ranged between 15,000 and 25,000 per cubic millimeter. Daily transfusions of whole blood were being given, but the patient began to have febrile reactions following some of these, and it was believed that these reactions would become more frequent with additional transfusions. At

Fig. 2.—Photograph of patient after splenectomy.

this time two bone marrow studies revealed active bone marrow with immature and agranular megakaryocytes and evidence of poor thrombocyte formation. Thus, it was decided that a splenectomy would be performed when and if the blood picture reached a plane within reasonably safe limits for a surgical procedure. At this date the infant had received 15 transfusions of whole blood.

On October 6, blood studies showed a sudden decrease in the bleeding time from 9 minutes 30 seconds on the previous day to 2 minutes and the erythrocyte count was over 4,000,000. This appeared to be the optimum time for surgical intervention, and a splenectomy was performed. The patient underwent the operation exceptionally well with no overt bleeding.

After surgical treatment, there was no spectacular rise in the thrombocyte count and the red blood cell count and hemoglobin content dropped critically. After one transfusion of 120 cc. of whole blood, there was a significant rise in the red blood cell count and hemoglobin value, but the thrombocyte count remained low. For several days postoperatively, the blood picture failed to show any improvement and daily blood transfusions were necessary to maintain the red cell count above a critical level. The bleeding time remained between 5 and 10 minutes. The hemangioma appeared to be growing larger and was reddened and tense. Within the next few days, however, a change occurred in the blood picture, as well as in the appearance of the hemangioma. On October 14 the red blood cell count was 5,300,000 per cubic millimeter, and, from that date until the date of discharge from the hospital three weeks later, the erythrocyte count remained between 4,250,000 and 5,500,000 per cubic millimeter without further blood trans-

fusions after October 12. The thrombocytes, however, continued to range between 10,000 and 20,000 per cubic millimeter and the bleeding time between 5 and 10 minutes. The hemangioma appeared somewhat smaller, the overlying skin was less tense and slightly wrinkled and the mass was softer in consistency (fig. 2).

The infant's general condition remained good until the time of discharge, with no further evidence of hemorrhage. The hemangioma had not shown an appreciable decrease in size on discharge.

Essential Laboratory Data and Blood Transfusions

Date	Red Blood Cells/ Cu. Mm.	Hemoglobin, %	White Blood Cells/ Cu. Mm.	Thrombocytes/ Cu. Mm.	Transfusions, Cc.
9/ 6/47	2,270,000	63.6	11,200	22,700	80
9/ 7/47	2,980,000	66	.....	17,880	80
9/ 8/47	4,100,000	80	.....	16,400	70
9/10/47	4,400,000	95.6	8,750	.....	..
9/11/47	4,490,000	87.6	.....	35,920	100
9/16/47	2,800,000	66	6,800	5,600	100
9/17/47	3,200,000	63.6	12,850	12,800	80
9/18/47	3,310,000	68.3	.....	19,860	..
9/19/47	3,810,000	66	.....	22,900	90
9/21/47	3,100,000	61.3	9,600	21,600	..
9/24/47	2,770,000	54.6	11,400	11,080	110
9/25/47	3,230,000	50	11,200	12,920	..
9/27/47	3,100,000	61.3	11,500	.....	130
9/29/47	3,280,000	68.3	.....	13,120	..
9/30/47	2,650,000	55	11,000	.....	120
10/ 1/47	4,190,000	77.6	.....	8,380	70
10/ 2/47	3,630,000	77.6	.....	14,520	70
10/ 3/47	3,760,000	77.6	.....	15,040	80
10/ 4/47	.....	....	.....	.....	120
10/ 5/47	3,880,000	70.6	.....	.....	120
Splenectomy					
10/ 6/47	4,940,000	87.6	13,100	8,600	50
10/ 7 47	2,670,000	39.6	.....	10,280	120
10/ 8/47	3,870,000	61.3	17,400	7,800	130
10/ 9/47	4,180,000	68.3	.....	None	110
10/10/47	3,980,000	70.6	.....	None	110
10/11/47	4,390,000	77.6	.....	None	..
10/12/47	3,920,000	68.3	.....	None	130
10/14/47	5,300,000	87.6	.....	10,600	..
10/16/47	5,440,000	98.3	15,700	10,000	..
10/18/47	6,150,000	101	14,500	12,300	..
10/21/47	5,550,000	117.6	.....	11,100	..
10/23/47	5,120,000	93	.....	20,400	..
10/27/47	5,120,000	93	.....	10,600	..
11/ 3/47	5,310,000	93	.....	18,000	..
11/14/47	4,870,000	82.6	.....	19,400	..
12/17/47	3,870,000	69.2	.....	3,870	..
3/20/48	4,260,000	75	.....	136,320	..
10/ 3/49	4,690,000	80	.....	235,000	..

On November 13 a second application of radium was made to the hemangioma by the tray method in a dosage of 300 mg. for one hour at 1 cm. over two areas on each side of the lesion.

On November 16 the patient was discharged from the hospital to be followed as an outpatient. Blood studies just prior to discharge revealed 4,870,000 red blood cells, 12 Gm. of hemoglobin, 12,900 white blood cells with a normal differential count, 19,400 thrombocytes, a bleeding time of 4½ minutes and a capillary coagulation time of 3½ minutes.

Subsequent blood studies revealed progressive improvement in the number of thrombocytes and erythrocytes as shown in the table.

The boy is now 3 years of age, has developed normally and manifests no evidence of blood dyscrasia. The hemangioma has shrunk so that now there remains only dark, brawny, pigmented skin at the site of the tumor (fig. 3).

COMMENT

In view of the fact that the causation of neither capillary hemangioma nor blood dyscrasias is adequately understood, it becomes impossible to discuss with any degree of assurance the true significance of the association of these two maladies. Silver and his co-workers [8] advanced three conflicting theories to explain the low thrombocyte count in thrombocytopenic purpura: (*a*) increased phagocytosis of the thrombocytes by the spleen and other reticuloendothelial tissues; (*b*) increased utilization of thrombocytes in an attempt to repair multiple capillary defects, and (*c*) decreased production of thrombocytes by the megakaryocytes in the bone marrow. These authors seemed to favor the last-mentioned theory as the most likely etiological factor in their case.

Fig. 3.—Photograph of patient at 3 years of age, showing residual pigmentation at site of tumor.

Similarly, we observed the presence of a large capillary bed due to the hemangioma for a long period before the blood dyscrasia became manifest. The hemangioma was present at birth, yet circumcision did not cause hemorrhage. Blood dyscrasia appeared at 6 weeks of age.

Our bone marrow studies showed immature and agranular megakaryocytes and poor thrombocyte formation.

It was our intention to right the blood picture by repeated blood transfusions, and only after febrile reactions intervened which threatened completely to disrupt the patient's chance for recovery was the drastic measure of splenectomy accepted. The response to splenectomy was slow and not dramatic; nevertheless, this procedure seemed to mark the turning point in the clinical picture, and we believe it was of benefit. If the cause of the purpura were excessive phagocytosis of the spleen, the response should have been more rapid and the decrease in erythrocytes and thrombocytes cannot thus be explained.

So few of these cases have been reported that we believe there is no high degree of association between blood dyscrasias and hemangioma, but that this case is merely

the coincidence of two separate disease entities. Many cases of hemangiomas have been reported, but few of these were associated with purpura. On the other hand, 36 cases of purpura in the newborn were reported recently by McAlenney and Kristan,[4] but these were not associated with hemangiomas.

The dosage of roentgen irradiation is well discussed by Rhodes and Borrelli,[2] but here again so few patients have been treated that the dosage is not well understood. It has been suggested that possibly roentgen therapy of sufficient dosage might suffice, but in the case reported the condition seemed too grave to withhold transfusions and splenectomy.

SUMMARY

A case of profound disturbance of the blood picture and marked diffuse purpura of the entire body, associated with a hemangioma, is reported.

Bleeding diathesis was not present at birth, as evidenced by no untoward reaction following circumcision. Purpura and blood dyscrasia appeared at 6 weeks of age. Twenty-one blood transfusions were given with febrile reactions encountered after the eighteenth and twentieth transfusions. Splenectomy was resorted to after four weeks of unsuccessful effort to alter the blood picture. After splenectomy, there was not the sharp rise in thrombocyte count expected in essential thrombocytopenic purpura but rather a slow rise of the deficient blood cellular elements and a gradual return to normal levels.

CONCLUSIONS

Hemangioma associated with blood dyscrasias occurs infrequently. The patients previously reported on have been treated by roentgen irradiation or by roentgen and radium irradiation and transfusions. Splenectomy may be necessary as a last resort if other measures fail. Further observations and reports would possibly help to clarify some of the suggested problems.

Dr. E. C. Weise, of the Department of Dermatology, Dr. B. M. Parmelee, of the Department of Roentgenology, Drs. I. L. Harshbarger and M. H. Eddy, of the Department of Surgery, and Dr. I. B. Akerson, of the Department of Pathology, aided in this study.

4. McAlenney, P. F., and Kristan, J. J.: Thrombopenic Purpura in Newborn: Review of Literature and Report of 6 Cases, Am. J. Dis. Child. **78**:401 (Sept.) 1949.

CONGENITAL OBLITERATION OF THE BILE DUCTS

Report of a Case Treated Successfully by Anastomosis of the Hepatic Ducts to the Duodenum

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AND
PHILLIP E. ROTHMAN, M.D.
LOS ANGELES

The excellent review of congenital malformations of the bile ducts by J. B. Holmes [1] in 1916 stimulated interest in the surgical correction of these conditions. He analyzed 120 reports which had appeared in the literature and concluded that a successful operation was theoretically possible in about 16 per cent of all cases. Accordingly, early exploration was strongly advised and is now generally practiced.

The clinical manifestations of this disorder have been described adequately in the many articles on the subject and in all textbooks on pediatrics. Jaundice in the newly born appears most commonly as a result of icterus neonatorum and erythroblastosis fetalis. Syphilis and sepsis are less frequent causes. A few instances of cholelithiasis in this age group have been reported. Biliary obstruction due to inspissated bile or mucus is often associated with a congenital stenosis of the bile ducts. Successful treatment by simple probing of the ducts or by saline irrigations has been accomplished by many surgeons. Complete biliary obstruction may occur as a rare complication of erythroblastosis fetalis. It results either from blockage of one of the larger bile ducts with inspissated bile or from swelling of damaged hepatic cells. This condition has been discussed by Lightwood and Bodian,[2] and recently a case has been observed at the Children's Hospital in Los Angeles. The child was proved to have erythroblastosis. Jaundice became intense and the stools were completely acholic. His condition improved spontaneously during a period of weeks, and at the age of 4½ months he was symptom-free. Intermittent biliary obstruction may be encountered when the anomaly consists of a cystic dilatation of the common duct (choledochus cyst). A few cases of viral hepatitis of the newborn have been observed by Wolman and his associates.[3] They believe that the infection occurs via the placenta before or at the time of birth.

Recently a patient presenting an unusual type of malformation of the bile ducts has been operated on by one of us (W.J.N.).

A white girl aged 2 months and 18 days, was referred to us by Dr. Newell Moore, of Santa Ana, with the diagnosis of congenital obliteration of the bile ducts. A faint jaundice, noted at birth, had become progressively more intense. The stools were always clay colored.

On examination the child was severely jaundiced but in fairly good condition. She weighed 9 pounds (4,080 Gm.), a gain of 2 pounds 6 ounces (1,087 Gm.) over the birth weight. The liver was palpable 3 cm. below the costal margin. The stools were completely acholic, and the urine contained bile. The hemoglobin content was 11.9 Gm.; the white blood cell count was 19,050, of which 74 per cent were lymphocytes. The Kahn reaction was negative. The bleeding and coagulation time were within normal limits.

From the Children's Hospital.

1. Holmes, J. B.: Congenital Obliteration of the Bile Ducts, Am. J. Dis. Child. **11**:405 (June) 1916.

2. Lightwood, R., and Bodian, M.: Biliary Obstruction Associated with Icterus Gravis Neonatorum, Arch. Dis. Childhood **21**:209 (Dec.) 1946.

3. Wolman, I. J.; Farquahar, J., and Stokes, J.: The Pathology of Congenital Hepatitis in the Infant, read before the Sixtieth Annual Meeting of the American Pediatric Society, French Lick, Ind., May 1950.

Laparotomy was performed on the day following admission through an upper right rectus muscle-splitting incision, with the patient under open ether anesthesia. Exploration disclosed abnormalities limited to the extrahepatic biliary system. The gallbladder was collapsed and extremely small and contained no bile. Leading from the gallbladder was a fibrous strand (fig. 1) that was patent for about the proximal third of its extent, as demonstrated by the

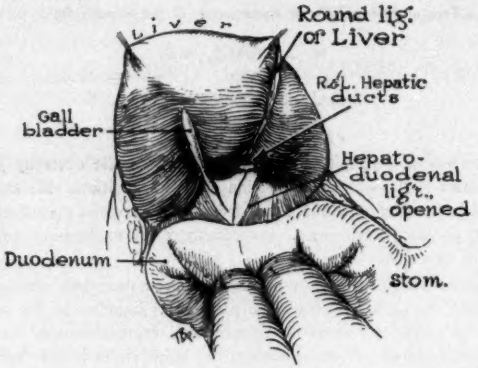

Fig. 1.—Diagrammatic representation of congenital obliteration of the bile ducts.

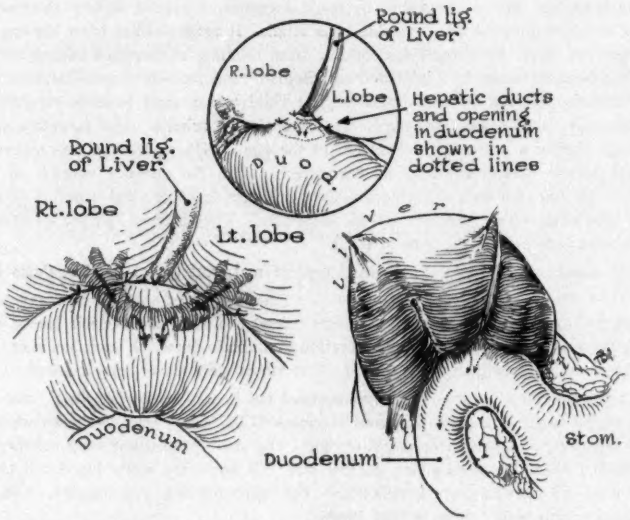

Fig. 2.—The anastomosis of the duodenum to the hepatic ducts.

injection of air into the gallbladder. The remaining contiguous strands proved to be solid cords. Each hepatic duct was approximately 4 mm. in diameter and contained bile as disclosed by needle puncture.

The duodenum was sutured to the fibrous tissue about the hepatic portal posterior to the hepatic ducts by interrupted fine cotton. The distal aspect of the ducts was then removed with scissors, allowing a free flow of bile (fig. 2). An incision was made through all layers of the duodenum 0.5 cm. anterior to the original line of sutures. The duodenum was fixed

anteriorly about the hepatic ducts with similar sutures. No biliary leakage following the anastomosis was apparent. The size of the hepatic ducts did not permit the placing of a tube within them. All structures of the abdominal wall except the skin and subcutaneous tissue were closed by figure-of-eight sutures of stainless steel wire. The skin was closed with interrupted fine dermal sutures.

The immediate postoperative course was somewhat stormy. The fluid and electrolyte balance was maintained parenterally, and penicillin was given. Bile drainage appeared in the gastric suction drainage 24 hours after the operation. On the third postoperative day, the infant retained feedings and the suction was discontinued. The stools became colored on the second or third day. The patient was discharged on the fourteenth postoperative day. She appeared well except for residual jaundice.

Examination at the age of 2 years and 4 months revealed a robust child in excellent health. Her weight was 29 pounds 4 ounces (13.3 Kg.), and her height was 36½ inches (92.7 cm.). The liver could not be palpated. She was completely free of jaundice and had no digestive difficulties.

Holmes's theoretical estimate of the operable cases of malformations of the bile ducts has been substantiated by Donovan,[4] Ladd [5] and others. In view of the successful result obtained in the operation described herein, one may regard all cases with patent hepatic ducts as amenable to surgical correction. The theoretical estimate of potential cures based on Holmes's diagrammatic illustrations would therefore increase to slightly over 50 per cent. If the hepatic ducts are not patent, the possibility has been considered that intrahepatic cholangiojejunostomy might offer a means of correction. However, the present opinion of Longmire,[6] who devised this procedure, is that the operation has little to recommend it in this type of case.

SUMMARY

A case of congenital malformation of the bile ducts is reported in which the duodenum was sutured around the hepatic ducts. By the application of this procedure to similar cases, a successful outcome is theoretically possible in 50 to 60 per cent of all cases of congenital anomalies of the bile ducts.

1136 West Sixth Street (17).

3875 Wilshire Boulevard (5).

4. Donovan, E. J.: Congenital Atresia of the Bile Ducts, Ann. Surg. **106**:737 (Oct.) 1937.

5. Ladd, W. E.: Congenital Obstruction of the Bile Ducts, Ann. Surg. **102**:742 (Oct) 1935.

6. Longmire, W., and Sanford, M. C.: Intrahepatic Cholangiojejunostomy with Partial Hepatectomy for Biliary Obstruction, Surgery **24**:264 (Aug.) 1948; Intrahepatic Cholangiojejunostomy for Biliary Obstruction—Further Studies, Ann. Surg. **130**:455 (Sept.) 1949.

EMPIRICAL ADMINISTRATION OF BAL IN ONE CASE OF POLIOMYELITIS

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ALTHOUGH much progress has been made in the understanding of the epidemiology of poliomyelitis, as yet no drug effective in treatment has been found.[1] In the past few years the drug dimercaprol (BAL) has come into prominence as a treatment against certain metallic poisons. This drug was first synthesized by Peters and his co-workers to counteract the effects of arsenical war gases. Present knowledge concerning this chemical has been recently reviewed by Randall and Seeler.[2] Dimercaprol is effective in heavy metal poisoning because it combines with the metals and protects certain enzymes, those containing a sulfhydryl group, from combination with the poison. Since viruses appear to be obligatory intracellular parasites and since they seem to cause necrosis by destroying or inhibiting certain intracellular enzyme systems, it was hypothesized that this preparation might be effective in the treatment of poliomyelitis. Because the drug has known toxic properties and occasionally causes marked discomfort to the patient,[3] it was decided to use the drug only in a case of severe bulbar involvement. The following case report gives the results of treatment.[4]

REPORT OF CASE

L. C., a 4½ year old girl, was well until Sept. 4, 1949, when she vomited several times and became rather drowsy and a slight fever developed. Two days later, difficulty in swallowing was first noticed and she appeared more ill to her mother. The next day her mother noted that the child had a paralysis of the left side of the face and that a great deal of mucus had accumulated in the child's throat. Accordingly, a physician was called who diagnosed bulbar poliomyelitis, and the patient was admitted to Englewood Hospital on September 8.

Physical examination on admission revealed temperature, 102. F.; pulse rate, 130; respiration rate, 34; blood pressure, 90/70. The patient was conscious but appeared quite ill. There were

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Associate Attending Physician, St. Vincent's Hospital.

1. Lawson, R. B.: Recent Concepts Regarding the Treatment of Poliomyelitis, New England J. Med. **239**:994-997 (Dec. 23) 1948. Paul, J. R.: Poliomyelitis: Early Diagnosis and Early Management of Acute Cases, Ann. Int. Med. **30**:1126-1133 (June) 1949; Poliomyelitis in Japan, Am. J. Hyg. **45**:206-218 (March) 1947.

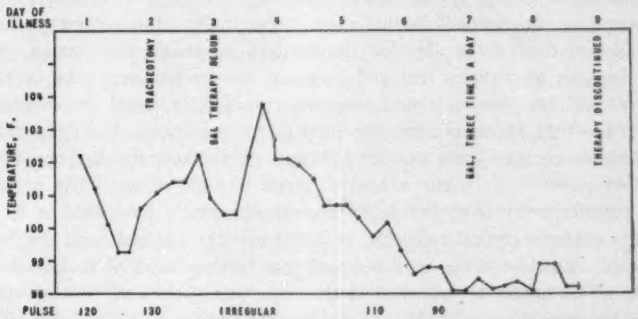
2. Randall, R. V., and Seeler, A. O.: Medical Progress: BAL, New England J. Med. **239**:1040-1045 (Dec. 30) 1948.

3. Durlacher, S. H.; Bunting, H.; Harrison, H. E.; Ordway, N. K., and Albrink, W. S.: Toxicological Action of 2,3-Dimercaptopropanol (BAL), J. Pharmacol. & Exper. Therap. (supp.) **87**:28-32 (Aug.) 1946. Modell, W.; Chenoweth, M. B., and Krop, S.: Toxicology of 2,3-Dimercaptopropanol (BAL) in Cats, ibid. **87**:33-40 (Aug.) 1946.

4. Treatment in this case was done through the cooperation of Dr. James P. Ward and Dr. John Gulash of the staff of Englewood Hospital, Bridgeport, Conn.

paralysis of the left side of the face and inability to close the left eyelid. The tongue deviated to the left. There appeared to be paralysis of the pharyngeal musculature. The heart and lungs were normal. Because of the seriousness of her condition, complete muscle testing was not done, but no gross paralysis of an extremity was noted. The laboratory examination on admission showed the urine to be normal. The red blood cell count was 3,870,000; the white blood cell count, 14,500, with 74 per cent polymorphonuclear leukocytes, 15 per cent lymphocytes, 6 per cent eosinophils and 5 per cent monocytes. Lumbar puncture revealed the spinal fluid to contain 40 cells per cubic millimeter, with 82 per cent lymphocytes and 12 per cent polymorphonuclear leukocytes. The blood sugar level was 125 mg. per 100 cc., and the protein level was 32 mg.

The child was placed in an oxygen tent and treated expectantly with parenteral fluids and aspiration of the mucus in the pharynx. On September 9 her condition became worse. Rales throughout both lung fields were noted, and a tracheotomy tube was inserted. By September 10 she was in deep coma and could not be aroused; respirations were rapid and shallow, and the pulse was too irregular to determine. A progress note read "the patient appears toxic and moribund." At noon September 10 administration of dimercaprol injection U. S. P. (BAL in oil) intramuscularly was begun. Dosage was calculated for the initial dose at 3 mg. per kilogram of body weight, and after that she received 0.15 cc. of the 10 per cent solution intramuscularly every four hours, or 2.5 mg. per kilogram, until September 13. On September 14 and 15 she received 0.15 cc. three times a day, and use of the drug was stopped on the 16th. On September



Temperature response and course, beginning Sept. 8, 1949, during dimercaprol therapy.

14 moderate periorbital edema developed. However, the patient had been receiving 2,000 cc. of fluid parenterally a day for 48 hours, and the foot of the bed had been elevated. The edema cleared in 24 hours.

The temperature response is illustrated in the chart. Twenty-four hours after administration of the drug was begun, the patient was able to respond to questions and open her eyes and move her arms and legs. By September 13 there was considerable improvement. The patient was able to swallow and take fluids, and the next day she was able to hold books in her hands and take semisolid food. On September 16 there was a slight rise in temperature (99.4 F.) that seemed to correspond with the appearance of thick yellow mucus in the trachea. On September 18 the tracheotomy tube was plugged off, and on September 20, it was removed and the temperature returned to normal. On September 22 the patient was transferred to the convalescent wing of the hospital. At the present time the child has complete use of all extremities. There is no evidence of facial or pharyngeal paralysis. The child is mentally alert and seems to have made a complete recovery.

COMMENT

This patient apparently suffered no ill effects from the use of dimercaprol and experienced no ill effects from the injection. It is doubtful that the transitory facial edema was the result of dimercaprol. Within 12 hours after the administration of the drug there was a sharp rise in temperature. This, however, would seem

to correspond more with the patient's clinical condition than with any effect of the compound. The dosage of 2.5 mg. per kilogram of body weight is in accord with the recommendation of the Council on Pharmacy and Chemistry of the American Medical Association. The number of injections she received a day were slightly greater than their recommended number.

If glutathione and other sulfhydryl containing enzymes and tissue protein can be injured by heavy metals, it seems quite possible that they can combine with and be injured by other substances besides metals. Similarly, it is quite possible that since dimercaprol contains two sulfhydryl groups, it may protect the enzymes from these nonmetallic toxic agents. This was the hypothesis behind the use of this drug in this case. As far as can be ascertained, this is the first time dimercaprol has been used in the treatment of poliomyelitis. After this patient was treated a communication from Dr. T. E. Boyd of the National Foundation for Infantile Paralysis revealed that some work had been done with the drug in relation to neurotropic virus infection in rodents and that there was no evidence of the efficiency of dimercaprol.

Bulbar poliomyelitis is a notoriously unpredictable disease. Recovery or death may ensue at any stage of the illness. No claim is made in this article for the effectiveness of dimercaprol in this case. Nevertheless, the patient's course was steadily downhill until the day that dimercaprol injections were begun. She had already been in an oxygen tent and had had the tracheotomy tube in place for 24 hours, and her condition had been deteriorating. Clinical improvement was manifested within 24 hours after the start of the injections, and temperature fall and return to consciousness rapidly followed. Unfortunately, the opportunity to treat other patients or to run a control series has not arisen. The physician in private practice away from university centers is severely hampered in his opportunities to perform clinical research. It is felt that the rational basis for the use of dimercaprol in poliomyelitis is sound and that further work should be done with the drug. This article is published in the hope that such work will be stimulated and that better evaluation of dimercaprol and its efficacy in poliomyelitis and other serious virus infections will be undertaken.

CHRONIC PANCREATITIS IN CHILDHOOD

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AND
WESTON M. KELSEY, M.D.
WINSTON-SALEM, N. C.

CHRONIC pancreatitis in childhood is a rare disease as judged by the paucity of reports in the literature. Standard texts [1] describe it but briefly. The disease does not present a typical clinical picture, although there are some symptoms which may be found in most cases. Severe epigastric pain is common, and clinically detectable ascites may occur, although it is rare. While in acute pancreatitis an elevated serum amylase level is a diagnostic point,[2] the persistence of an elevated serum amylase level in chronic pancreatitis is unusual. The lack of a typical clinical picture probably accounts for a number of cases which undoubtedly remain undiagnosed. This report presents a case of chronic pancreatitis in an 8 year old boy whose primary complaint was marked ascites and who maintained a persistently elevated serum amylase level for six months after the clinical picture had returned to normal.

REPORT OF A CASE

M. W., an 8 year old white boy, was admitted to the North Carolina Baptist Hospital with a history of a swollen abdomen of three weeks' duration. The onset of the illness was 14 weeks before admission, at which time he became weak and lost weight. Eight weeks prior to admission, the boy began to have attacks of severe pain in his epigastrium. These attacks frequently were accompanied with vomiting. The attacks were not precipitated by any particular foods, and they did not occur at regular periods, although they were probably commoner after breakfast. The pain awakened the patient from sleep on several occasions. The attacks rarely lasted over an hour at a time, and the boy felt relatively well in the intervals between them. These attacks recurred persistently until the patient was admitted to the hospital, but they had decreased in frequency from several attacks daily to two or three attacks weekly. During the height of the attacks the stools became soft, mushy and almost white. Three weeks prior to admission, the parents first noticed the appearance of abdominal distention. The distention increased gradually until 13 weeks after the onset of the present illness, at which time the patient was admitted to the local hospital because of the abdominal swelling. Three liters of a

From the Department of Pediatrics of the Bowman Gray School of Medicine of Wake Forest College and the Pediatric Service of the North Carolina Baptist Hospital.

1. Holt, L. E., and McIntosh, R., cited in Holt, L. E., and Howland, J.: Diseases of Infancy and Childhood: A Textbook for the Use of Students and Practitioners, ed. 11, New York, Appleton-Century-Crofts Company, Inc., 1939. von Pfaundler, M., and Schlossmann, A.: The Diseases of Children: A Work for the Practicing Physician, translated by M. G. Peterman, Philadelphia, J. B. Lippincott Company, 1935. Mitchell, G., and Nelson, W.: Textbook of Pediatrics, ed. 5, Philadelphia, W. B. Saunders Company, 1950.

2. (*a*) Elman, R.: Blood Amylase in Relation to Disease of the Pancreas: Further Observations, Arch. Int. Med. **48**:828 (Nov., pt. 1) 1931. (*b*) Sorkin, S. Z.: Blood Amylase Activity in Disease of Carbohydrate Metabolism and in Non-Diabetic Pancreatic Disease, J. Clin. Invest. **22**:329 (May) 1943.

reddish fluid were withdrawn by abdominal paracentesis. The fluid reaccumulated rapidly, and another liter of the same type of fluid was removed three days later. The boy was then referred to the North Carolina Baptist Hospital for further diagnostic studies.

The patient had had mumps two years prior to the onset of the present illness. He had a history of episodes of vomiting in infancy and very early childhood, but no direct relation to the present illness could be established. No history of jaundice or previous abdominal distention could be obtained.

Physical Examination.—On admission the boy appeared chronically ill. The oral temperature was 37.2 C. (99 F.). The pulse rate was 144 a minute. The blood pressure was 118/50. The skin over the upper extremities showed evidence of considerable wasting. The veins over the anterior part of the chest and abdomen were moderately dilated. There was minimal pitting edema in the legs. Abdominal distention was marked, and a fluid wave was present. The liver and spleen were not palpable.

Laboratory Data.—Blood studies on admission showed a hemoglobin level of 14 Gm. per 100 cc. of blood, 4,900,000 red blood cells per centimeter, and 11,500 white blood cells per centimeter. The differential blood cell count was within normal limits. The corrected sedimentation rate according to Wintrobe's method was 32 mm. in one hour. Urine was normal on six examinations. Intradermal tuberculin test reactions were negative to 0.1 mg. of old tuberculin,

Serum Amylase Levels *

Date	Post-operative Day	Days After Onset of Ascites	Serum Amylase Level, Somogyi Units
10/28/47	5	35	362
10/31/47	8	38	401
11/ 6/47	14	44	348
11/10/47	18	48	330
11/28/47	36	66	422
12/29/47	67	97	323
2/23/48	121	151	190
6/ 7/48	8 mo.	9 mo.	123

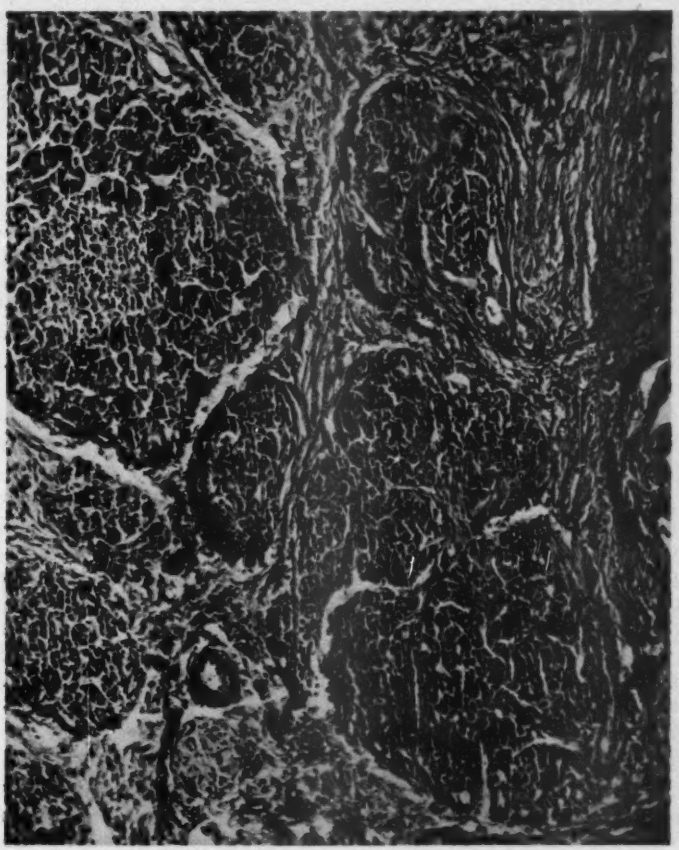
* The successive serum amylase levels reveal the persistence of a high level for at least two months, with a gradual decline afterward to a slightly elevated level nine months after onset of the ascites.

and the reactions to the tuberculin patch test were negative. The specific gravity of the ascitic fluid was 1.011, and a blood cell count of the fluid revealed 160,000 red blood cells per centimeter. Microscopic examination of the fluid showed no other significant findings, and all cultures were sterile. Blood nonprotein nitrogen was 30 mg. per 100 mg. The specific gravity of the urine was 1.022. Serum proteins totaled 5 Gm. per 100 cc. Sulfobromophthalein liver function test revealed no retention of dye 30 minutes after injection. Serum bilirubin was 0.1 and 0.5 mg. per 100 mg. The results of the urea clearance test were within normal limits. Stool examinations revealed no excess fat or starch, and no parasites were found. Serum amylase level determinations are listed in the table.

Roentgenograms.—Flat plate of the abdomen, roentgen studies of the entire gastrointestinal tract and intravenous pyelograms revealed no pathological condition.

Course in the Hospital.—An abdominal paracentesis was performed immediately on admission of the patient to the ward, and 6,600 cc. of homogeneous reddish fluid was removed. This procedure relieved the patient, but he complained periodically of severe abdominal epigastric pain during the following nine days. There was no fever. Exploratory laparotomy was performed on the ninth hospital day, with the expectation of finding some form of portal vein obstruction since there had been reaccumulation of the fluid. Firm nodules were found in the head of the pancreas at operation, and biopsies were obtained. The postoperative course was uneventful. Beginning on the seventeenth postoperative day, the patient was given fractional doses of high voltage roentgen ray therapy, 116 roentgen units to his epigastrium on three successive days. There was no reaccumulation of fluid, and the boy was discharged on the twentieth postoperative day.

Operative Note.—The peritoneum was entered, and immediately a geyser of amber-colored fluid spurted up through the incision, the total amount of the fluid measuring 4,900 cc., not including, however, several hundred cubic centimeters which escaped suction. The omentum was found to be stuck to the anterior peritoneum above the umbilicus over an area about as wide as the hand. From this radiated several adhesive bands which were very vascular and which included several loops of small bowel. The liver was explored and found to be normal. The spleen was small and normal to palpation. The stomach contained no demonstrable abnormality,



Sections of pancreatic tissue in which islets and glandular cells were present.

and the duodenum was normal. The pancreas was not enlarged, but the head contained several nodules which were slightly firm, and a biopsy was made of these. The small bowel was explored from the ligament of Treitz to the ileocecal valve and found to contain only the sites of adhesive bands. There were no other abnormalities. The colon was normal.

Microscopic Pathology Report.—A section of pancreatic tissue in which the islets and glandular cells were present is shown in the figure. The glandular elements occurred in small islands, and there was considerable scarring between and around the islands. The diagnosis was chronic pancreatitis with scarring.

Follow-Up.—The patient has been followed for 12 months, and there has been no return of ascites. His appetite has been normal. He had occasional episodes of abdominal pain for six months after discharge from the hospital. Since that time he has had no complaints. Serum amylase levels have been persistently elevated but have been decreasing gradually.

REVIEW OF LITERATURE

Three cases of chronic pancreatitis in childhood have been found reported in the literature. Two of these cases were reported in a study of chronic relapsing pancreatitis by Comfort, Gambill and Baggenstoss.[3] Collett and Kennedy[4] described a case of chronic relapsing pancreatitis associated with hyperlipemia in an 8 year old boy. Some pediatric textbooks do not mention the existence of chronic pancreatitis in childhood, and in those that do, only a few lines are devoted to discussion of the disorder.

The etiology of chronic pancreatitis is not entirely understood. Opie[5] classified the etiological factors in chronic interstitial pancreatitis in the following way: obstruction of pancreatic ducts with resulting retention of secretion, pancreatic calculi, biliary calculi with obstruction of the ampulla of Vater, malignant growth, ascending infection, vascular alterations within the pancreas, tuberculosis, syphilis and alcohol. More recently, regarding pancreatic calculi, Comfort[6] expressed the belief that stones in the ducts result from pancreatitis rather than cause it, and he presented roentgenologic evidence that, in several case studies, the onset of clinical symptoms preceded the appearance of calcification. Comfort and others[3] listed alcohol as a probable etiological factor in a number of their cases and mentioned Giardia lamblia infection and infection of the common bile duct (common channel hypothesis) as possible factors in a few other cases.

Symptomatology of the three cases found in the literature includes a varied array of findings. However, in all three cases severe epigastric pain, intermittent but brief and accompanied with nausea and vomiting, was the predominant symptom. Food precipitated attacks of pain in one of the cases reported by Comfort and others.[3] Weight loss, emaciation and later on edema and ascites occurred in the other. Hepatomegaly and light colored, bulky stools were present in one of Comfort's two cases and also were described by Collett and Kennedy.[4] In the latter case, hyperlipemia accompanied the pancreatitis and the boy revealed xanthomatous lesions of the skin; the fatty acids in the stools were increased to 10 times normal, the blood serum was chylous and the phospholipid and cholesterol levels were markedly elevated. Serum amylase levels were normal or only slightly elevated in all three cases, but external pancreatic secretion was diminished in one. Calcifications of the pancreas were discovered by roentgenogram in one of the two patients described by Comfort and others,[3] and these were later removed at operation. This

3. Comfort, M. W.; Gambill, E. E., and Baggenstoss, A. H.: Chronic Relapsing Pancreatitis: A Study of 29 Cases Without Associated Disease of Biliary or Gastro-Intestinal Tract, Gastroenterology **6**:239 (April) 1946.

4. Collett, R. W., and Kennedy, R. L. J.: Chronic Relapsing Pancreatitis Associated with Hyperlipemia in an 8 Year Old Boy, Proc. Staff Meet., Mayo Clin. **23**:158 (March 31) 1948.

5. Opie, E. L.: Disease of the Pancreas: Its Cause and Nature, ed. 2, Philadelphia, J. B. Lippincott Company, 1910, pp. 15 and 200.

6. Comfort, M. W.: Chronic Relapsing Pancreatitis: Its Clinical Course, Sequelae, Diagnosis and Medical Treatment in Cases in Which Disease of Biliary or Gastro-Intestinal Tract Did Not Coexist, Proc. Staff Meet., Mayo Clin. **22**:548 (Nov. 26) 1947.

boy also received roentgen ray therapy to the pancreas. Two of the patients survived, and at autopsy of the patient who expired extensive atrophy of the pancreatic acini with both interlobular and intralobular fibrosis was found.

While chronic pancreatitis in childhood has been infrequently reported, 35 cases of acute pancreatitis in the pediatric age group were found reported in the literature,[7] and there are, no doubt, others. In one case of acute pancreatitis described by Dobbs,[7e] the urinary diastase level remained elevated for a month after clinical recovery. Shallow and Wagner [7i] reported another case in which the serum amylase level was elevated to 180 Somogyi [8] units or more 20 days after recession of clinical symptoms.

Much has been written regarding secondary pancreatitis which follows in the wake of an acute infection such as mumps parotitis. Véghelyi [9] described cases in which the pancreatitis was preceded by parotitis and scarlet fever, and he mentioned that cases had been reported in association with typhoid, spirochetal jaundice, diphtheria, malaria, pneumonia and influenza. In one of the cases reported by Véghelyi,[9] death occurred over two years after the initial parotitis and as a termination of a long period of pancreatic insufficiency.

COMMENT

The unusual aspects of our case are threefold. First, chronic pancreatitis is rare in childhood. This is borne out by the paucity of reports in the literature. Second, the presenting complaint in our case was ascites. Although ascites has been reported in chronic and acute pancreatitis,[10] it is rarely a major symptom. The presence of the marked ascites in this case and its recurrence after drainage suggested obstruction of the portal system. Consequently, it was not until after operation that the clinical picture could be attributed to the pancreatic disease. The finding of the pathological condition of the pancreas at operation led to the determination of serial serum amylase levels. Third, the initial elevated level and the persistence of this elevation were considered unusual. Sorkin [2b] noted a persistent elevation of the serum amylase in an adult patient with carcinoma of the head of the pancreas. Pinkham [11] stated that chronic pancreatitis per se does not usually give a sustained

7. (*a*) Adams, A. W.: Traumatic Pancreatitis in Child, Brit. M. J. **2**:854 (Oct. 28) 1939. (*b*) Desjacques, R.: Acute Hemorrhagic Pancreatitis in a 5 Year Old Child, Lyon méd. **149**:255 (Feb. 28) 1932. (*c*) Dobbs, R. H.: Acute Pancreatitis in Childhood: Report of a Case, Lancet **2**:989 (Nov. 2) 1935. (*d*) Eliason, E. L., and North, J. P.: Acute Pancreatitis, Surg., Gynec. & Obst. **51**:183 (Aug.) 1930. (*e*) Jaeger, H. W.: Acute Pancreatitis in Children, Rev. chilena de pediat. **14**:18 (Jan.) 1943. (*f*) Lynch, K. M.: Pancreatitis: An Analysis of Types and Causes, Ann. Int. Med. **14**:628 (Oct.) 1940. (*g*) Schmieden, V., and Sebening, W.: Surgery of the Pancreas, Arch. f. klin. Chir. **148**:319, 1927. (*h*) Sujoy, E.: Hemorrhagic Pancreatitis in an 8 Year Old Girl, Prensa méd. argent. **23**:1224 (May 13) 1936. (*i*) Shallow, T. A., and Wagner, F. B., Jr.: Traumatic Pancreatitis, Ann. Surg. **125**:66 (Jan.) 1947.

8. Somogyi, M.: Micromethods for the Estimation of Diastase, J. Biol. Chem. **125**:399 (Sept.) 1938.

9. Véghelyi, P. V.: Secondary Pancreatitis, Am. J. Dis. Child. **74**:45 (July) 1947.

10. Elman, R.: Acute Interstitial Pancreatitis: Clinical Study of 37 Cases Showing Edema, Swelling and Induration of Pancreas but Without Necrosis, Haemorrhage or Suppuration, Surg., Gynec. & Obst. **57**:291 (Sept.) 1933.

11. Pinkham, R. D.: Pancreatic Collections (Pseudocysts) Following Pancreatitis and Pancreatic Necrosis: Review and Analysis of 10 Cases, Surg., Gynec. & Obst. **80**:225 (March) 1945.

elevation of the serum amylase. Also, Cantarow and Trumper [12] remark that normal serum amylase levels are the rule in chronic disorders of the pancreas, including chronic pancreatitis.

The cause of the pancreatitis in our patient was not definitely determined.

That chronic pancreatitis may follow the episode of acute pancreatitis seems likely. Baggenstoss [13] stated that chronic relapsing pancreatitis may represent the summation of repeated attacks of acute interstitial pancreatitis, or repeated sublethal attacks of so-called hemorrhagic pancreatitis or perhaps, in some cases, a combination of the two types. In discussing disease of the pancreas, Wightman [14] expressed the belief that chronic pancreatitis may be insidious and steadily progressive in development, or, in some cases, it may consist of a series of acute attacks. In view of the relatively frequent occurrence of acute pancreatitis in childhood as compared with the chronic disorder, it is highly probable that the incidence of the latter condition actually is greater than one would suspect from a review of the literature. The lack of a typical clinical picture may be contributory to the failure of diagnosis of such cases.

The treatment of our patient with roentgen ray therapy followed the recommendation of a visiting consultant [15] who referred us to Morton's [16] report of nine cases of acute pancreatitis treated with roentgen ray. The response of our patient to the therapy suggested that the treatment may have been beneficial. Comfort and others [3] reported the use of roentgen ray therapy in one of their cases of chronic pancreatitis.

SUMMARY

A case of chronic pancreatitis in an 8 year old boy is reported. Only three cases of chronic pancreatitis in childhood were found in the literature.

Marked ascites and persistently elevated serum amylase levels were unusual features.

It is suggested that there is a greater incidence of chronic pancreatitis in childhood than has been previously recognized.

12. Cantarow, A., and Trumper, M.: Clinical Biochemistry, ed. 4, Philadelphia, W. B. Saunders Company, 1949.

13. Baggenstoss, A. H.: Chronic Relapsing Pancreatitis: A Review of Pathologic Anatomy in Cases in Which Disease of Biliary or Gastro-Intestinal Tract Did Not Coexist, Proc. Staff Meet., Mayo Clin. **22**:542 (Nov. 26) 1947.

14. Wightman, K. J. R.: Diseases of the Pancreas, M. Clin. North America **32**:518 (March) 1948.

15. Dr. Wingate Johnson.

16. Morton, J. J.: Acute Pancreatitis, Surgery **17**:475 (April) 1945.

OSTEOPETROSIS (MARBLE BONES)

Report of a Case with Special Reference to Early Roentgenologic and Pathological Findings

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OSTEOPETROSIS (Albers-Schönberg [1] disease) is a rare condition in which the normal bony structure becomes thickened and sclerotic because of an increase in the number and size of the trabeculae and excessive calcareous deposit.

McCune and Bradley [2] in a critical review of the literature up to 1934 found 69 cases which could be considered as due to this disease. By 1941 Higinbotham and Alexander [3] were able to collect 135 cases including their own, and by 1947 Pines and Lederer [4] had increased the number of reported cases to 148. In the past three years we were able to find 26 additional reported cases, making the number 174 up to 1950. The confusion of this disease, especially in the earlier days, with various other bone conditions, notably certain cases of osteopoikilosis, melorheostosis and osteosclerosis from fluorine or phosphorus poisoning or myelosclerosis, makes it difficult in some cases to render a true evaluation of the roentgen findings. It may be reliably accepted, however, that the number of reported cases certainly does not exceed the number stated. The very rarity of the disease requires reports of all cases in order that as much material is available for study as possible. This case is reported because of certain pathological and roentgenologic findings noted early in the disease which may be of significance. Most biopsy specimens are taken from patients in whom the bone changes are well established; on this account they may be of limited value in determining the method of onset of the disease.

ETIOLOGICAL ASPECTS

The cause of the disease is not known, but a strong familial tendency and indications of a hereditary background are recorded. Consanguinity seems to play a definite part in some cases, especially the marriage of cousins. Numerous instances of the disease have been reported in the same family.[5]

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1. Albers-Schönberg, H.: Roentgenbilder einer seltenen Knochenerkrankung, München. med. Wchnschr. **51**:365, 1904.

2. McCune, D. J., and Bradley, C.: Osteopetrosis (Marble Bones) in an Infant: Review of Literature, Am. J. Dis. Child. **48**:949 (Nov.) 1934.

3. Higinbotham, N. L., and Alexander, S. F.: Osteopetrosis: Four Cases in One Family, Am. J. Surg. **53**:444, 1941.

4. Pines, B., and Lederer, M.: Osteopetrosis: Albers-Schönberg Disease (Marble Bones); Report of Case and Morphological Study, Am. J. Path. **23**:755, 1947.

5. (*a*) Kelley, C., and Lawlah, J. W.: Albers-Schönberg Disease: A Family Survey, Radiology **47**:507, 1946. (*b*) Pirie, A. H.: The Development of Marble Bones, Am. J. Roentgenol. **24**:147, 1930; (*c*) Marble Bones, ibid. **30**:618, 1933.

The possibility of fluorine poisoning as an etiological factor has often been considered,[6] perhaps owing more to the similar chalky appearance of the bones in both conditions than to any actual bearing on the cause. If fluorine poisoning were the cause, calcium fluoride crystals should be observed in the haversian systems, and these are lacking.

CLINICAL MANIFESTATIONS

There are a few distinctive clinical signs or symptoms.

Gradual encroachment of the sclerotic bone on the medullary canal, causing depletion of the bone marrow results in reduction in the blood-forming structure to the point of profound anemia. The progressive anemia produced in this manner is the principal cause of the constitutional manifestations and of the short span of life of persons with this disease.

The blood and other laboratory findings were reviewed with such care by McCune and Bradley [2] in 1934 that further detailed analyses would seem superfluous. Since that time, little of significance has been added. The changes found in the blood picture vary widely, not only among different persons but in the same person at different times. These differences are probably due to the variation in the extent of bone marrow depletion, although in some cases the changes do not seem to run parallel. In general, there is definite reduction in the red blood cell count, with even greater proportionate reduction in hemoglobin content, resulting in a color index of less than unity. The white blood cell count is usually reduced, but the differential count may vary widely.

The serum calcium is usually normal or slightly elevated, but this value is rarely above 12 mg. per 100 cc. (Some cases, however, have been reported in which the value was doubled.[7]) Blood phosphorus is usually normal; the phosphatase may be decreased. The bone marrow becomes pale and fibrotic and is lessened in amount as the sclerotic bone continues to invade the medullary cavity.

The urine shows little consistent change. Later in the disease the blood pressure may be elevated. The basal metabolic rate is usually unaltered.

ROENTGEN MANIFESTATIONS

Diagnosis of the disease is dependent on the roentgen manifestations. The desirability of separation of the cases into those of infants and young children during the growth period and those of older persons in whom the disease is fully established has been emphasized.

In the infantile growing stage the condition has been reported as present at birth and even while the fetus was still in utero.[8] In many instances, however,

6. Speder, E.: L'ostéopétrose généralisée ou "marmorskelett" n'est pas une maladie rare; sa fréquence dans l'intoxication fluorée, J. radiol. et électrol. **20**:1, 1936; abstracted, Am. J. Roentgenol. **38**:506, 1937.

7. Schulze, F.: Das Wesen des Krankheitsbildes der "Marmorknochen (Albers-Schönberg)," Arch. klin. Chir. **118**:411, 1921.

8. (*a*) Clifton, W.; Frank, A., and Freeman, S.: Osteopetrosis (Marble Bones), Am. J. Dis. Child. **56**:1020 (Nov.) 1938. (*b*) Jenkinson, E. L.; Pfisterer, W. H.; Latteier, K. K., and Martin, M. E.: Prenatal Diagnosis of Osteopetrosis, Am. J. Roentgenol. **49**:455, 1943.

the bony structures appear normal at birth and not until a few months or even a year has passed do the characteristics of the disease become evident.[9] At this time the growing bone in the diaphysial regions begins to show an unusual increase in density, which progresses to involvement of the entire shaft (fig. 5). At first this gives an appearance of dense sclerosis in the metaphysial region similar to that seen associated with poisoning by heavy metals, such as phosphorus or lead, or to that which develops with the healing of rickets after vitamin D administration. As the condition progresses, however, the sclerosis does not fade off into normal bone density but continues into the shaft, and its true nature soon becomes evident. Parallel longitudinal striations appear in the cancellous ends of the long bones, fading out as they approach the compact portion of the shaft. This causes widening of the ends of the long bones or "clubbing" (figs. 5 and 7). As the sclerotic condition extends into the more compact shaft, there is less variation in the contour or size of the normal bone structure.

In the older, fully established stage all the bony parts assume a structureless dense appearance (figs. 6 to 10). Most of the thickening of the bone takes place by encroachment on the medullary canal. In some cases numerous transverse lines appear in the diaphysis, running across the ends of the bones and suggesting a periodic interference with growth. Instances have been reported[9] in which the disease process, previously well established, has been suspended for a considerable period, as indicated by a resumption of normal bone formation at the epiphyses. This was not brought about by any medication or change in diet or surroundings.

Encroachment of the thick sclerotic bone on the medullary cavity reduces not only the size of the marrow space but also the size of the nutrient canals, thus depleting the blood supply to the bone. Such a state of the bony structure may result in spontaneous infractions wherever the bone is at a strain (fig. 9). The regions most frequently affected are the under side of the femoral neck and the upper ends of the tibial condyles where weight-bearing stress is greatest. Such infractions are most pronounced in persons in whom there is a natural tendency to coxa vara deformity; this is followed by upper tibial infractions when the infractions of the femoral neck result in excessive strain being transferred to the lower part of the leg from the resulting knock knee deformity. In those patients who have a tendency to coxa valga, such infractions of the femoral neck do not seem to occur. Multiple infractions of the femoral neck seem to involve mainly the inferior portion, with the superior portion of the neck left intact. This results in normal undisturbed epiphysial growth of the upper portion and suspension of growth of the inferior portions of the neck, producing extreme coxa vara and knock knee deformity. This seems to be unavoidable, since application of an abduction cast or other fixation apparatus to prevent the deformity would have to be maintained for such a long period that it would be impractical.

The bones are usually extremely hard, in some cases sufficiently so "to turn the edge of a steel chisel or drill"; in other instances[5b, c] they have been found to be soft and brittle, more of the consistency of chalk. Owing to the brittleness of the bones, there is a tendency to spontaneous fractures. These are often acquired without any history of trauma and may cause little inconvenience, especially if

9. Fairbank, H. A. T.: Osteopetrosis: Osteopetrosis Generalisata, Marble Bones, Albers-Schönberg's Disease, Osteosclerosis Fragilitas Generalisata, J. Bone & Joint Surg. **30-B**:339, 1948.

incomplete. They may be discovered quite by accident on roentgenologic examination. In some reported cases multiple fractures have been an outstanding clinical feature of the disease. Reports vary on the rapidity and effectiveness of healing; in some cases repair is prompt with firm new bone formation; in others, healing is delayed over a long period, sometimes a year or more (figs. 2 and 10).[10]

The osteosclerosis associated with the disease affects the skull as well, and encroachment on the cranial orifices may cause nerve pressure and loss of function. Optic atrophy or deafness may result from this process. Clubbing enlargement of the posterior clinoid processes of the sella turcica may encroach on the pituitary fossa so that it crowds the pituitary gland. This may be a factor in the tendency to dwarfism which sometimes accompanies the disease.

Numerous other diseases of widely varying character have been reported as accompanying this condition. Perhaps one of the most frequent of these is fluorine poisoning. The dense sclerosis of the bones resulting from both these conditions is, no doubt, one of the principal reasons for the assumption that they may have some common etiological factor.[11] The exposure to fluorine from drinking water in the present patient was an interesting side light but probably of no etiological significance.

Hodgkin's disease has been reported as a condition complicating marble bones.[12]

Associated bacterial infection has previously been recognized as a grave complication. An instance has been reported in which the lower jaw became infected, followed by osteomyelitis and complete extrusion of the mandible as a sequestrum.[13] Bernhardt[14] has reported a case in which amputation was performed because of osteomyelitic infection. In these days of antibiotic therapy infection is no longer such a dreaded complication.

Bone sarcoma has been encountered in association with osteopetrosis, but there was no indication that this was in any way due to the disease.[15]

Rickets has been reported many times as an accompaniment of marble bones.[16] In such circumstances the rachitic reaction may be somewhat unusual; in addition to the epiphysial changes ordinarily observed in rickets, heavy periosteal reaction is seen investing the entire bony shaft like a cloak.

Obviously, there is no special reason that a person with osteopetrosis may not also have any other disease.

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10. Alexander, W. G.: Marble Bones with Review of Literature, Am. J. Roentgenol. **10**:280, 1923.

11. Winter, G. R.: Albers-Schönberg Disease: Report of 2 Cases, Am. J. Orthodontics (Oral Surg. Sect.) **31**:637, 1945.

12. Herscher, H., and Stein, J. J.: Osteopetrosis Associated with Hodgkin's Disease: Review of Literature and Report of Case, Am. J. Roentgenol. **43**:74, 1940.

13. Shallow, T. A.; Davis, W. B., and Farrell, J. T.: Osteopetrosis, Ann. Surg. **100**:512, 1934.

14. Bernhardt, H.: Ein Beitrag zur Marmorknochenerkrankungen, Klin. Wchnschr. **5**:415, 1926.

15. Kerr, H. D.: Case of Osteopetrosis (Marble Bones) Complicated by Osteogenic Sarcoma, Am. J. Roentgenol. **35**:212, 1936.

16. (*a*) Karshner, R. G.: Osteopetrosis, Am. J. Roentgenol. **16**:405, 1926. (*b*) Kramer, B., and Halpert, B.: Marble Bones: Clinicopathologic Observations, Am. J. Dis. Child. **57**:795 (April) 1939. (*c*) Kudrjawtzewa, N.: Über Marmorknochenkrankheit, Arch. klin. Chir. **159**: 658, 1930. (*d*) McCune and Bradley.[2]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis must be considered under two headings: the infantile stage, when the disease is in the process of development, and the older, more advanced stage, after the disease is fully established.

In the infantile stage, during the period of actual growth, osteopetrosis must be differentiated from rickets, scurvy and congenital syphilis (the infantile diseases of most frequent occurrence); the results of vitamin D administration (cod liver oil or its extracts); heavy metal poisoning (lead, phosphorus, bismuth, etc.); acute infantile cortical hyperostosis.

Rickets in the stage of active development offers no problem, but in the healing stage after heavy doses of vitamin D the dense zone in the diaphysial region may simulate that seen in marble bones. This is especially true because of the generalized involvement of all the bones of the body. The head, too, may be large in rickets, lending a certain similarity in appearance. However, in osteopetrosis the changes present in all other portions of the bones serve to differentiate the condition. Likewise, rickets is transitory; on assumption of a regular diet it soon disappears. A number of cases have been reported in which rickets was associated with well developed osteopetrosis.[17]

Scurvy in its healing stage may show an apparent sclerosis of the shaft of a bone during calcification of an extensive subperiosteal hemorrhage. Such a sclerotic appearance is irregular, however, and usually affects only one or two bones.

Congenital syphilis may give some trouble, especially since the fetus in both diseases may be born macerated.[8b] When congenital syphilis goes untreated, the pathological manifestations primarily present in the bony structure subside only to recur several years later as heavy periosteal deposits along the shafts of the bones, extending over the epiphysial ends, which may resemble osteopetrosis. Furthermore, practically all the long bones are involved. It will be evident, however, that the bone production is due to a periosteal reaction in this disease, not merely to sclerosis as in osteopetrosis. Periosteal reaction is not an outstanding feature of osteopetrosis. Vitamin D administration, as of cod liver oil or any of its extracts, especially when hyperphosphated, produces a heavy zone of increased density at the epiphysial line. This affects all bones but usually is closely confined to the epiphysial region and does not extend up the shaft.

Poisoning with heavy metals, such as lead, phosphorus or bismuth, likewise produces bands of increased density in the epiphysial region, but these also tend to remain localized. They are accompanied with other signs of toxicity and a history of exposure. Bismuth given as a therapeutic agent to the mother during pregnancy may show as zones of increased density in the epiphysial regions in the baby after birth. The width of the zone is determined by the length of time of administration. The density is never as great as that seen in marble bones, and the line of demarcation is abrupt.

Acute infantile cortical hyperostosis is an unusual disease, thought to be infectious because of the fever which accompanies it. It comes on suddenly, is associated with dense sclerosis of the shaft or entire bone structure but involves usually only a few bones. It heals spontaneously after a few months.

17. Footnote 16 *a* and *c*. McCune and Bradley.[2]

Hypothyroidism may produce a uniform increase in density of all the bones similar to that of osteopetrosis, but the other clinical manifestations of cretinism readily establish the diagnosis.

In the stage of fully developed osteopetrosis, after the entire bony structure has become sclerotic, the diagnosis is usually quite simple. The condition must be differentiated only from those few diseases that produce a dense homogeneous sclerosis of all the bones. These are fluorosis from fluorine poisoning and myelosclerosis from fibrotic replacement of the bone marrow and subsequent increased calcium deposition of unknown causation.

These diseases, of course, occur primarily in adults. No heavy metal other than fluorine will be deposited in sufficient quantities in adult bone to increase its roentgenographic density. History of exposure to fluorine, often through drinking water, checkering of the teeth and demonstration of calcium fluoride crystals in the haversian canals will serve to establish a diagnosis.[11]

Myelosclerosis, while it may produce something of the same appearance, is also accompanied with fibrous replacement of the bone marrow with consequent blood changes, but the sclerosis is never as dense, and the condition soon becomes fatal.[18]

MICROSCOPIC CHANGES

Numerous reports have been made on biopsy specimens from the bones of persons of different ages showing the disease in different stages of development. The variation revealed in the microscopic pictures probably is explained by this diversity of material. Prof. Waugh's description of the specimen taken from the knee of Pirie's [8b, c] patient, a 14 year old girl, is fairly representative of the findings of others.

Section taken so as to include epiphysis, epiphyseo-diaphyseal line and diaphysis presents the following picture: the epiphysis shows relatively normal appearing cancellous bone composed of spicules with very little enclosed cartilage. Between the spicules there is a large amount of relatively hemorrhagic myeloid tissue containing considerable fibrillar matrix. As one approaches the epiphyseo-diaphyseal line there are greater inclusions of cartilage in the bony spicules. The line varies considerably in thickness, showing a firmer, lighter staining, more compact area of cartilage towards the epiphysis and a more cellular cartilaginous zone which varies considerably in thickness towards the diaphysis. The histological structure of the diaphysis is distinctly different from that of the epiphysis. It impresses one as being fundamentally calcified cartilage in which are smaller and larger irregular open spaces. These open areas compose less than 25 per cent of the total structure and are lined by irregular masses of bony tissue. Scattered throughout the calcified cartilaginous material are innumerable small spherical foci of ossification completel, surrounded by it so that no open space is present. This arrangement persists well out to the periosteum though there is present a narrow irregular zone of subperiosteal compact bone. Compared with the epiphysis, the diaphysis is here much less vascular. The open spaces contain rather cellular, irregular, fibroblastic strands, but few typical myeloid cells. Flattened osteoblasts are conspicuous about the lining of the spaces, but typical osteoclasts are comparatively rare.

Beyond the end of the bone as one enters the shaft the ossification is much more complete, the open spaces are much larger and myeloid cells are found in them. Even here, nevertheless, there is an abnormal amount of cartilage in the bony spicules and there is a relatively large amount of osteoid tissue. Here a definite zone of compact bone of considerable thickness is present beneath the periosteum.

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18. Rosenthal, N., and Erf, L. A.: Clinical Observations on Osteopetrosis and Myelofibrosis, Arch. Int. Med. **71**:793 (June) 1943.

Most pathologists agree that the bony structure is densely sclerotic with invasion or complete replacement of the fatty bone marrow by fibrous tissue. Osteoblasts predominate; few osteoclasts are present, and these may completely disappear as the disease becomes fully established. The trabecular arrangement is disorderly, and calcium deposition may be excessive.

REPORT OF CASE

L. J. H., a white girl, was 3½ months old at the time of her first admission. She resided in a small community near El Paso, Texas. Strangely enough this community had a high fluorine content in the drinking water, and we had previously seen a person with fluorine poisoning from

Fig. 1.—Upper extremities of an infant 3½ months old (Jan. 16, 1940), showing few distinguishing characteristics of osteopetrosis at this early age. Note two ossification centers for bones of wrist. There is ordinarily little change in epiphysial development. Courtesy of Dr. P. C. Schnoebelen.

this same region. Both parents were in good health, and there was no indication of blood relationship. There was no evidence of this or any other bone disease in any member of the family; a sister born later showed no signs of bone disease. At birth the present infant seemed normal; at 6 weeks of age, however, the head was noticeably enlarged. This was the first indication of abnormality.

The patient was first seen Jan. 7, 1940 at the age of 3½ months, because of listlessness, weakness and enlargement of the head, thought to be due to rickets or possibly hydrocephalus. On roentgen examination an increase in density was noted in some of the bony structures, especially in the diaphysial regions, but the disease had not yet assumed its characteristic appearance. Two centers of ossification were already present in the wrist (fig. 1). The skull was large but did not show any distinctive features at that time.

A bone biopsy specimen was taken by Dr. Phil Sherer on January 18 from the lower portion of the right femur. On drilling the shaft there was no bleeding. A granular substance was all that was found in the marrow cavity. The bones were not hard, and the bone drill penetrated without pressure; it was impossible to tell when it entered the marrow cavity.

The immediate pathological report on bone specimen stated that the specimen consisted of several small bits of bone from the right femur. Section showed some osteoblastic activity and considerable replacement of the marrow by loose, rather vascular infiltration, especially around the vessels. The impression of the examiner, Dr. B. C. Portuondo, was osteoperiostitis.

While the etiological basis was not definitely recognized, the possibility of syphilis was suggested. It will be seen, then, that at this early stage of development recognition of the disease was not possible from even the biopsy specimen. The roentgen findings were also inconclusive, showing increased density only at the epiphysial regions, with some periostitis. On the basis of

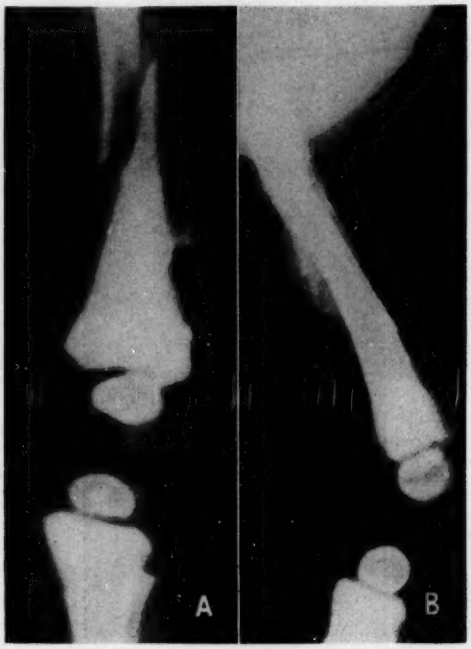


Fig. 2.—*A*, spontaneous fracture through the shaft of the femur two months later (March 13), well above the site of previous removal of biopsy specimen, which can be recognized by the periosteal new bone on the outer side of the femur just above the epiphysis. *B*, healing of fracture with large amount of new bone formation approximately one month later (April 19). This is in contradistinction to the scant new bone formation and prolonged healing time of a spontaneous fracture of the femur at 8 years of age shown in figure 9. Courtesy of Dr. P. C. Schnoebelen.

this pathological diagnosis, in spite of a negative Wassermann reaction, the infant was given antisyphilitic treatment for the next four months; other supportive measures, such as diet and iron therapy for anemia, were also undertaken. It was felt that the Wassermann reaction might be unreliable in early infancy.

Two months after biopsy (March 13, 1940) a spontaneous fracture occurred just above the operative site (fig. 2 *A*); the fracture was long and oblique and in the midportion of the shaft of the femur. A roentgenogram taken 10 days later (March 23; fig. 2 *B*) showed new bone formation; the ends of the bones displayed an increase in calcium and the shaft a decrease. Within

five weeks (April 19) roentgen examination revealed complete union with an "enormous amount of callus."

Laboratory findings at that time were as follows: The hemoglobin concentration was 58 to 72 per cent. Red blood cells numbered 3,340,000 to 3,690,000. The color index was 0.9 to 0.8. The white blood cell count was 4,500 to 7,500, with a differential count showing 1 to 3 per cent basophils, 1 to 5 per cent eosinophils, 2 to 4 per cent juvenile cells, 7 to 14 per cent stab forms, 11 to 17 per cent segmented cells, 59 to 64 per cent lymphocytes and 4 to 6 per cent monocytes. Microcytes, macrocytes and polychromasia were observed. Blood cholesterol measured 84 mg., blood calcium 12.4 mg., blood phosphorus 4 mg., nonprotein nitrogen 27 mg., and sugar 96 mg., per 100 cc. The Wassermann reaction was negative. The urine showed no casts, albumin or blood.

The second admission was nine months after the first (September 22). In the meantime the patient had been treated for syphilis. There was no apparent change from the results on previous

Fig. 3.—Bone specimen removed at 3½ months of age at an early stage in the development of the disease. Note bone marrow surrounded by newly formed bone trabeculae. Bone marrow spaces are occupied by vascular inflammatory tissue with dense perivascular lymphocytic infiltration and few giant cells. Bone trabeculae are lined with osteoblasts, densely calcified.

examination. The head was still large, and the child showed little change in appearance. Definite improvement was noted in the blood picture. The hemoglobin concentration was 90 per cent. Red blood cells numbered 4,220,000. The color index was 1.0. The white blood cell count was 10,100, with a differential count of 1 per cent stab forms, 28 per cent segmented cells, 61 per cent lymphocytes and 6 per cent monocytes. Inorganic phosphates measured 4.8 mg. per 100 cc. The Wassermann reaction was negative.

By this time the bone lesions on roentgen examination were sufficiently advanced to suggest the true nature of the disease, and a diagnosis of "osteosclerosis, probably due to Albers-Schönberg disease," was made by Dr. P. C. Schnoebelen.

The final pathological report on the microscopic section taken on the first admission (at age of 3½ months) given in greater detail by Prof. William Bauer, of St. Louis University, and Dr. Portuondo was as follows:

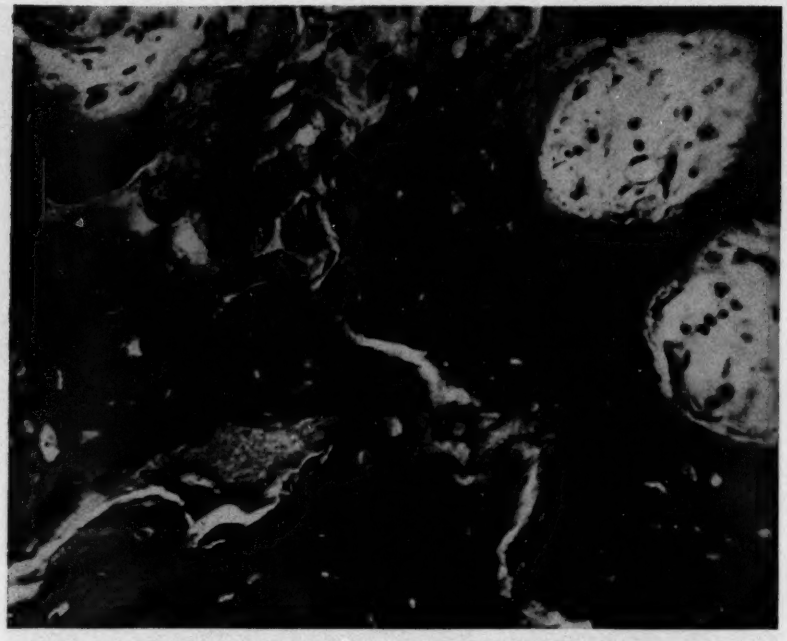


Fig. 4.—Necrotic bone between densely calcified bone trabeculae. Note many empty osteocytes, irregular calcification and loose connective tissue in bone marrow spaces.

Fig. 5.—As the disease progresses, a dense sclerotic zone appears along the diaphysial side of the epiphysial line which gradually extends to involve the entire shaft. Dark longitudinal lines appear within the calcifying bone which probably represent columns of uncalcified cartilaginous cells.

"The bone marrow was surrounded by newly formed bone trabeculae. The bone marrow space was occupied by vascular inflammatory tissue with dense perivascular lymphocytic infiltration and a few giant cells. The bone trabeculae, lined with osteoblasts, were densely calcified (fig. 3). Necrotic bone was seen between the densely calcified bone trabeculae. Many empty osteocytes, irregular calcification and loose connective tissue in bone marrow spaces were noted" (fig. 4).

No fluoride crystals were seen in the sections.

Fig. 6.—The bones soon assume a structureless chalky appearance. The cancellous ends of the bones, having a weaker cortical structure, permit bulging of the outline of the bone from pressure of hyperplasia and hyperactive calcification of the bone. This gives a "club-shaped" appearance to the ends of the bones.

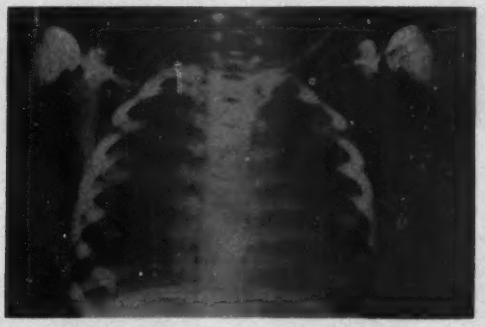


Fig. 7.—Chest and shoulders. Note dense structureless appearance of all bones of thorax and clubbing of upper portions of humeri.

Since that time (a period of over 10 years) the patient has been followed at intervals, still showing the typical appearance of marble bones (figs. 5 to 11).

At 8 years of age deafness began to develop and has become slowly progressive; there has been, however, no evidence of optic involvement.

At this age it became evident that she had suffered somewhat in growth, being several inches shorter than her younger sister. Otherwise she enjoyed good health.

Later on a second fracture of the femur occurred through the shaft (fig. 6) spontaneously, without definite history of trauma; function was not suspended, the child continuing to walk and play during the entire period of repair. The incomplete character of the fracture made this possible, although it did increase the liability of making the fracture complete. Only very slight

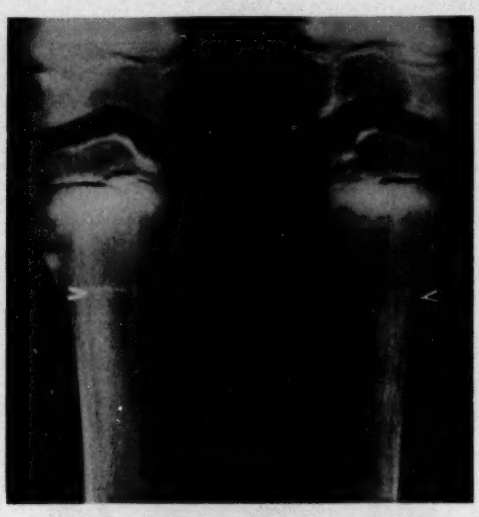


Fig. 8.—In some instances dense transverse lines appear across the diaphysial ends of the bones, indicating short periods of remission of the disease. Such remissions have been reported.

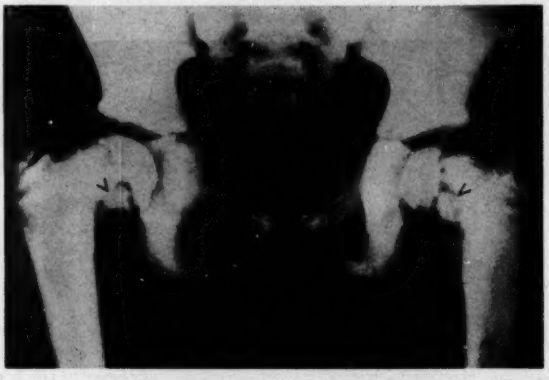


Fig. 9.—Spontaneous infractions of the lower margins of the necks of both femurs due to stress and strain on bone at this point. Upper part remains intact and continues its normal growth while the lower part does not grow. This gives rise to extreme coxa vara and knock knee deformity.

periosteal bone occurred over the first seven months, and the line of fracture was not completely filled in with new bone for more than a year. Similarly, the infractions which occurred in the femoral neck showed little evidence of repair over an extended period.

Fig. 10.—Spontaneous transverse fracture occurred in shaft of femur at about 8 years of age. Fracture was incomplete, developed only scant new bone and required over a year to heal. Contrast with rapid healing of previous fracture (fig. 2) which occurred in infancy. Note that the infractions of the femoral necks have also healed but with marked coxa vara deformity (see fig. 9).

Fig. 11.—The phalanges after 10 years are the slowest bones to show replacement of the normal bone structure with that of sclerotic marble bones.

TREATMENT

No treatment so far tried has been effective in modifying the course of the disease. Intervals of reversion to normal bone growth have been observed by Fairbank,[9] but he has been unable to determine any change of environment, medication or diet which might have influenced the disease.

One might speculate that depletion of vitamin D in the diet might result in decrease in calcium content of the bones. Yet in reported cases in which rickets was associated, there was no indication that the lack of vitamin D affected the osteopetrosis.

In some cases, in well advanced stages of the disease, the posterior clinoid processes of the pituitary may produce a squeezing effect on the pituitary gland. In no case was there indication of change in pituitary function, so that endocrine treatment of this sort probably could not be expected to produce any variation in the disease.

Hyperparathyroidism from tumor of the parathyroid gland failed to have any material influence on the disease, as indicated in a reported case.

COMMENT

A review of all the pathological, roentgenologic and clinical manifestations of osteopetrosis indicates that it is primarily a disease of the bone cells and their growth. In our patient rapid healing of the fracture which occurred following removal of a biopsy specimen in the first few months of life, with abundant new bone formation, indicates almost hyperactivity of the osteoblasts; the smoothing out at the fracture site so that its location in later years could not be detected is indication of osteoclastic activity in the fulfilment of Wolff's law—at least during the early stage of bone growth.

Microscopic observations as noted in the literature indicate a gradual disappearance of the osteoclasts as time goes on and the bone becomes completely involved. It is possible that the osteoblasts also may ultimately decrease in number and activity, as indicated by the small amount of callus which develops about a fracture occurring in the well advanced stage of the disease and the prolonged period necessary for its union.

The perivascular lymphocytic infiltration so evident in the bone sections made in our patient at 3½ months of age may be of significance in the speculation on the site of first involvement of the disease. Might it not be possible that the perivascular infiltration occurred in response to some unusual infection or other bodily reaction, and that this may be the underlying cause in the development of the disease, the osteosclerosis and calcium deposit following a generalized depletion in blood supply due to the initial disorder? As for the hereditary tendency and the part played by consanguinity in the occurrence of the disease, may it not be possible that some type of incompatibility between the elements of the blood and a specific tissue like the bone or bone marrow is transmitted, similar to the Rh factor in pregnancy?

POINTS OF INTEREST

This case is of interest for several reasons. The first is the improvement from a state of severe anemia within four months, as a result of ordinary treatment, such

as iron therapy, diet and hygienic measures. It is difficult to understand how such simple measures could have such a decided effect. In the years that followed, the blood picture has been maintained in a fairly satisfactory state without difficulty.

Second, the soft character of the bone taken for biopsy may be explained by the the fact that it was from the lower cancellous end of the femur early in the disease. This suggests that perhaps the hardness of the bone is dependent on the age of the patient, the site from which it was taken and the duration of the disease.

Third, the comparison of bone reaction in two fractures, one occurring following the removal of the biopsy specimen in early infancy, which healed with abundant bone formation within one month, and the other which occurred spontaneously in the middle third of the shaft at 8 years of age after the disease was well established, in which bone repair was scant and slow to form, requiring more than a year for complete healing, suggests that perhaps the reparative process is directly dependent on the softer, less sclerotic character of the bony structure.

The fourth point is the multiple infractions or incomplete fractures of the under surface of the necks of the femurs and the condyles of the tibias which interfered locally with epiphysial growth, resulting in coxa vara and extreme bowleg deformity. Perhaps the reduction in blood supply produced by encroachment on the nutrient artery may have an unfavorable influence on the nutrition of the bone and healing of fractures. The trabeculae seem heavy with a purposeless arrangement, suggesting that Wolff's law may not be followed normally in bone repair.

Fifth, the relative avascularity of the bone marrow, even at this early stage in the development of the disease, and the perivascular lymphocytic infiltration which was evident everywhere throughout the specimen may prove to be significant findings in the determination of site of origin and method of development of the disease.

Sixth, the coincidence of exposure to fluorine by means of drinking water is interesting, since poisoning by this material has been suspected as an etiological factor in the disease almost from the time of its first description.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

SENSITIVITY OF DIPHTHERIA BACILLI AND RELATED ORGANISMS TO NINE ANTIBIOTICS. GEORGE GEE JACKSON, M.D.; CHANG, SHIH-MAN, M.D., and EDWIN H. PLACE, J. Pediat. **37**:718 (Nov.) 1950.

Nine antibiotics were tested in vitro against a number of strains of diphtheria bacilli. On a weight basis, the order of their activity was as follows: (1) bacitracin, (2) penicillin, (3) terramycin, (4) chloramphenicol (chloromycetin), (5) neomycin, (6) aureomycin, (7) streptomycin, (8) aerosporin, (9) polymyxin. From these results one may surmise that aerosporin and polymyxin are not suited for therapy against these organisms. Bacitracin and neomycin can be used only locally. Effective plasma concentrations of penicillin, terramycin, chloramphenicol, aureomycin and streptomycin can be maintained, and these drugs may have therapeutic potentialities.

MACDONALD, Pittsburgh.

Metabolism; Infant Feeding; Milk and Other Foods

BREAST FEEDING COMES OF AGE. FRANK HOWARD RICHARDSON, J. A. M. A. **142**:863 (March 24) 1950.

Richardson reviews various contributions to breast feeding. Mothers should be taught manual expression to empty the breasts after nursing to obtain maximum production; complementary feedings should be used as necessary to keep mothers from worrying. Overfeeding adjusts itself. Use of both breasts at each feeding is better than alternate use of the breasts, and the length of each feeding as well as the schedule must be individualized. If the baby's head is higher than his stomach while he is nursing, he does not swallow so much air. The most formidable of all obstacles to breast feeding is the indifference and, at times, actual opposition of a large part of the medical profession.

KIMBALL, Evanston, Ill.

USE OF PARENTERAL POTASSIUM THERAPY IN SURGICAL PATIENTS: ITS ROLE IN PREVENTING CHLORIDE LOSS. CHARLES LOWE, MARGARET ROURKE, ELSIE MACLACHLAN and ALLAN BUTLER, Pediatrics **6**:183 (Aug.) 1950.

These balance studies supplement the observations of other investigators that in patients suffering fasting, dehydration and intracellular potassium depletion due to an alarm reaction or to an alkalosis resulting from loss of gastric chloride parenteral administration of isotonic sodium chloride solution may be ineffective in accomplishing extracellular repair, since sodium goes with water to the dehydrated and potassium-depleted cells, and chloride is excreted in the urine. When such therapy is modified by decreasing the ratio of sodium to water and adding potassium, there is a more physiologic hydration of both fluid compartments of the body, chloride being conserved by the kidneys and sodium tending to stay in its proper extracellular position. Similar conservation of urinary chloride and elevation in serum chloride has been noted to follow administration of potassium to patients with low serum chloride concentrations associated with ulcerative colitis, a situation in which excessive loss of potassium and chloride in the urine suggests a similar alarm reaction.

FROM THE AUTHORS' SUMMARY.

BIOLOGICAL TESTING OF MILK FOR TUBERCULOSIS AND BRUCELLOSIS. P. J. MEARS, South African M. J. **24**:593 (July 22) 1950.

Guinea pig inoculations were used to detect tuberculosis and brucellosis contamination of milk samples in the Johannesburg area. Tubercle bacilli were found in 1.02 per cent of the samples. Agglutination tests on the serum of the inoculated guinea pigs showed 16.1 per cent of the milk samples to be contaminated with brucella.

MCGUIGAN, Evanston, Ill.

THE pH OF MOTHER'S MILK. F. CACIOPPO, Pediatria **58**:371 (May) 1950.

The pH of many samples of mother's milk, immediately after expression and protected from exposure to air, was found to average 7.26. When the milk was exposed to air, it gradually became more alkaline. If the milk was kept protected from air by an oil covering, the pH shifted gradually in the acid direction.

HIGGINS, Boston.

INFANT'S DIET IN RELATION TO INTESTINAL FLORA. F. GABRERO GOMEZ, J. MONEREO GONZALEZ and B. TARACENA DEL PINTA, Acta pediat. españ. **87**:209 (March) 1950.

The investigators give the details of a study of the intestinal flora in all portions of the intestinal tract of 54 well and sick newborn infants with all types of feeding.

The organisms isolated were Bacillus coli in 68 per cent, Lactobacillus bifidus in 44.07 per cent, Enterococcus in 40.7 per cent, Bacillus proteus in 25.9 per cent, Staphylococcus (albus and aureus) in 18.5 per cent, Streptococcus lactis aerogenes in 14.4 per cent, paracolon bacilli 11.1 per cent, Neisseria orbiculata 7.6 per cent, Alcaligenes fecalis 5.6 per cent, Clostridium perfringens 3.8 per cent and Cryptococcus (Torula) 1.8 per cent. The authors also made a similar study on 50 white rats.

The authors concluded, briefly, that feeding is responsible for little difference between the intestinal flora. Lactobacillus bifidus was found in both sick and well infants receiving all types of feedings. They never succeeded in isolating this organism in aerobic conditions. In the rats and mice L. acidophilus, which is aerobic, predominated over the anaerobic lactobacillus bifidus. The authors were not able to prove the predominance of one organism over another in different feeding, although it would appear that L. bifidus is more abundant when the quantity of lactose in the milk product is greater.

The flora of children suffering from nutritional diseases of a nonspecific nature is similar in most respects to that of the normal chi'd. After the sterile meconium has passed, the intestinal flora of the feces in the newborn is almost identical with that of the nursing baby of 6 months of age.

Except in the stomach and the first part of the small intestine, there is no definite relation between the type of flora and the anatomical portion of the digestive tract.

ALLEN, Santa Fe, N. M.

PROTEIN DEFICIENCY IN A BREAST-FED INFANT. RUDOLF MEINERT, Monatsschr. Kinderh. **97**:482 (Jan.) 1950.

Meinert reports the case of a 3 month old breast-fed infant with marked generalized edema, anemia (2,600,000 erythrocytes and 46.5 per cent hemoglobin) and hypoproteinemia (2.6 Gm. of total serum proteins per 100 cc.). Since the protein content of the mother's milk was only 0.55 Gm. per 100 cc. (normal 1.3 to 1.6 Gm.), the diagnosis of alimentary protein deficiency was made. Congenital hepatic cirrhosis, nephrosis without albuminuria, and essential hypoproteinemia were ruled out in the differential diagnosis.

HARTENSTEIN, Madison, Wis.

PRESERVATION OF RAW HUMAN BREAST MILK WITH CITRIC ACID OR STREPTOMYCIN. HANS ROOS and MANFRED KINDLER, Monatsschr. Kinderh. **97**:494 (Jan.) 1950.

Addition of 600 mg. of citric acid or of 4 mg. of streptomycin per 100 cc. proved to be about equally effective in preserving raw unboiled human milk.

HARTENSTEIN, Madison, Wis.

Hygiene; Growth and Nutrition; Public Health

PEDIATRIC CARE UNDER THE NORTH CAROLINA PLAN. ARTHUR H. LONDON JR. and WILBURT C. DAVISON, J. A. M. A. **143**:1232 (Aug. 5) 1950.

A means of improving pediatric care in a rural area shows promise of working in North Carolina.

KIMBALL, Evanston, Ill.

PHYSICAL GROWTH OF SHANGHAI SCHOOL CHILDREN. T. G. NI, Chinese M. J. **67**:677 (Dec.) 1949.

To determine the effect of World War II on the nutritional status of Shanghai children Ni in 1945 obtained the heights and weights and their ratios—the nutritional quotient—of over 1,000 Shanghai school children, aged 4 to 11 years, from middle class families. The mean weights and heights of these children are definitely less than those of a similar group studied in 1939. In fact, the figures for the present group approximate those of a group of refugee children measured in 1938. The nutritional quotients of these children in 1945 differed only slightly from those of the Shanghai children studied in 1939 for the reason that the former group was smaller in stature as well as underweight.

Poor nutrition is the cause of this growth failure, according to Ni, and this poor nutrition is not due to lack of available foodstuffs; Shanghai had no such lack. Inflation and the rising cost of living made it impossible for the middle class Chinese to feed their children properly.

MACDONALD, Pittsburgh.

Newborn

RH-HR GROUP: ITS GENETICS AND NOMENCLATURE. A. B. ROY CHOWDHURY, J. Indian M. A. **19**:129 (Jan.) 1950.

This is a very brief paper which adds nothing to the understanding of the Rh problem.

MCGUIGAN, Evanston, Ill.

RH INCOMPATIBILITY: AN ANALYSIS OF 1320 INVESTIGATIONS. A. ZOUTENDYK, South African M. J. **23**:138 (Feb. 19) 1949.

This survey reiterates the need for routine Rh testing in all women, especially in the antenatal period. The author feels that many babies can thus be saved. Rh incompatibility is considered unimportant as a cause of repeated abortions in the early months of pregnancy.

MCGUIGAN, Evanston, Ill.

RH SENSITIZATION AND REPLACEMENT TRANSFUSION. MAURICE SHAPIRO, South African M. J. **23**:576 (July 9) 1949.

Present day knowledge of Rh sensitization is discussed at length and the immunologic aspects explored in detail. Therapy is presented only briefly. Shapiro apparently feels that replacement transfusion is the treatment of choice.

MCGUIGAN, Evanston, Ill.

AN EPIDEMIC OF DIARRHEA OF THE NEWBORN. L. CHASTRUSSE, Pédiatrie **36**:299 (July-Aug.) 1947.

In March 1946, there was a sudden outbreak of diarrhea among the babies of the obstetrical department of the André-Boursier Hospital in Bordeaux affecting 22 infants. Although a large number of cases of otitis media (an epidemic of 30 cases from January to April) occurred at that time, Chastrusse observed many cases of diarrhea in babies not showing any sign of ear infection. Between the fourth and thirteenth day frequent liquid yellow odorless stools were expelled forcefully with much gas. Most patients were not very sick, but some had a toxic appearance—they had some focus of infection (usually the middle ear and antrum), became rapidly dehydrated, vomited and showed moderate temperature elevation. Under correct treatment the condition of some improved in a few days, but in other children in spite of the best treatment diarrhea persisted and the child died athreptic and toxic or with a complication such as bronchopneumonia, abscess and so on.

Etiology.—Breast-fed and artificially fed infants were affected alike; the milk could therefore not be responsible. Parenteral infection, such as otitis media, was proved in only six of the 22 cases; therefore infection outside the intestinal tract could not be the cause either. Stool cultures still yielded no pathogens.

Epidemiology.—The means of transmission of the condition could not be established. The respiratory tract was considered, but the digestive tract was more likely to be the cause, especially since the soiled diapers were dried overnight on radiators and reused on different babies the next morning because of the shortage of linen.

Differential Diagnosis.—Chastrusse tries to differentiate the diarrhea he observed from other forms of diarrhea and finds that the type described by Lust and Nelis (*Bruxelles-méd.* **26**:173 [Feb. 24] 1946) resembles closely the above disease. The Belgian authors did not find any causative organism either. The mortality rate of their children was 40 to 50 per cent, and the only difference was that their children all appeared toxic and septic, which conditions were observed only in those with fatal cases of the epidemic in Bordeaux. The treatment consisted of mother's milk; dry milk or buttermilk; 125 cc. of isotonic sodium chloride solution or dextrose administered subcutaneously twice a day; sulfaguanidine, and myringotomy or antrotomy if necessary. Penicillin was given to three children with fatal cases.

GLASER, Chicago

FORWARD SUBLUXATION OF THE ATLAS FOLLOWING BIRTH TRAUMA. K. I. LOUNAVAARA, Acta pædiat. **37**:341, 1949.

Lounavaara describes a case of a 2 month old child in which an infected retropharyngeal hematoma following birth trauma caused a heavy laryngeal stridor and later, the stridor having lasted four weeks, as a secondary result a "spontaneous" forward luxation of the atlas which hitherto has not been described in a newborn child. He considers this subluxation to be caused by decalcification following infectious hyperemia. Based on the development of the disease, he establishes the reversibility of this process. At an autopsy performed immediately on death, confirmation of the diagnosis was facilitated by the presence of the hereditary heart disease.

FROM THE AUTHOR'S SUMMARY.

UNUSUAL CASE OF ANEMIA GRAVIS IN A NEWBORN INFANT. H. UHRBRAND, A. SØEBORG OHLSEN and E. FREIESLEBEN, Acta pædiat. **37**:349, 1949.

A case of severe megaloblastic anemia (hemoglobin, 20 per cent) in a 7 day old boy is described. The etiology is unknown. Blood group incompatibility cannot have been the cause, as mother and child were both Rh positive with identical Rh genotypes and the child belonged to blood group O. Intoxication as well as syphilis and other infections seemed to be out of question.

Blood transfusions were effective, whereas the effect of liver therapy was not convincing. The child recovered in two months.

FROM THE AUTHORS' SUMMARY.

PEMPHIGUS NEONATORUM IN MATERNITY HOSPITALS. GUNNEL MELIN and GÖSTA WALLMARK, Acta pædiat., 1949, supp. 75, p. 175.

During a minor epidemic of pemphigus neonatorum occurring in a maternity ward, bacteriologic investigations were carried out. The isolated staphylococci were typed with the aid of bacteriophages. The Staphylococcus causing pemphigus could not be put into the type scheme but reacted in a characteristic way to one bacteriophage. This same type also occurred in some healthy children and in the air and the floor dust.

Besides the members of the staff, the newly born babies also appear to have played a considerable part in spreading infectious agents.

The investigations carried out in a ward that was free from pemphigus yielded just as abundant staphylococci. The epidemiology of pemphigus neonatorum is discussed.

FROM THE AUTHORS' SUMMARY.

HYPOPROTHROMBINEMIA AND CEREBRAL LESION IN AN INFANT WHOSE MOTHER HAD BEEN TREATED WITH DICOUMARIN. GERT VON SYDOW, Nord. med. (Hygiea) **34**:1171 (May 16) 1947.

In a pregnant woman of 44 crural thrombosis developed which was treated with bishydroxycoumarin U. S. P. (dicumarol®) from September 25 to October 24, with a total dose of 1.75 Gm. On October 26, when delivery began, the prothrombin index was 33, and it decreased to a

minimum value of 16 two days later; then a large dose of vitamin K brought the prothrombin index to normal value. The delivery occurred as an anterior brow presentation and was accompanied with remarkably slight loss of blood. The birth weight of the infant was 2,600 Gm. According to routine it was given 1 mg. vitamin K immediately after birth. A few hours later the forehead and the scalp were found covered with extensive subcutaneous hemorrhages. The prothrombin index was less than 10. An injection of 10 mg. vitamin K was given without evident effect on the index. Repeated large daily doses of vitamin K both parenterally and perorally did not raise the prothrombin index until six days after birth, when it rapidly increased to normal values. From three weeks of life on, the infant showed increasing signs of internal hydrocephalus, which was supposed to be due to traumatic hemorrhages and connected with the hypoprothrombinemia. Von Sydow is of the opinion that the remarkable hypoprothrombinemia in this case was caused by the bishydroxycoumarin U. S. P. treatment of the mother during pregnancy.

WALLGREN, Stockholm, Sweden.

ASPHYXIA OF THE NEWBORN. YNGVE ÅKERRÉN, Nord. med. (Hygiea) **34**:1269 (May 30) 1947.

A critical survey of the pathogenesis, symptomatology and therapy of neonatal asphyxia with references to authoritative opinion in obstetric and pediatric circles in the United States is given by Åkerrén.

WALLGREN, Stockholm, Sweden.

BLOOD DESTRUCTION IN NEWBORN. J. ENGELHARDT, Maandschr. v. kindergeneesk. **15**:267 (Aug.) 1947.

After a short discussion of former theories about icterus neonatorum, Engelhardt gives a new theory on postnatal hemolysis based on experimental findings. He started from the theory of Bergenhem and Fåhraeus who believe that from circulating blood (spleen) lysolecithin is formed; this substance is produced from lecithin by the enzyme lecithinase. This lysolecithin causes hemolysis of the red blood cells.

The results of his investigations are listed below.

1. From incubated serum or plasma of cord blood more lysolecithin can be extracted than from incubated adult serum.

2. Serum or plasma of cord blood has a lesser hemolysis-inhibiting effect than does adult serum.

3. This hemolysis-inhibiting effect of serum is mainly due to its cholesterol content (cholesterol compounds with lysolecithin).

4. Estrone inhibits in vitro the formation of lysolecithin.

5. The degree of hemolysis during the first nine days is chiefly determined by the relation of the plasma lipids (lecithin: cholesterol) in cord blood. A higher lipid quotient goes with a more intense hemolysis.

6. This relation is disturbed in infants to whom was given 30,000 units of estrone intramuscularly during the first 24 hours. These infants showed a delayed rise of serum bilirubin and a less pronounced fall of their hemoglobin content.

From these results the theory was advanced that after birth blood destruction increases as a result of the excretion of estrone from the organism, which increase can be checked by the rising cholesterol content.

VAN CREVELD, Amsterdam, Netherlands.

A-O ANTAGONISM AND HEPATIC CIRRHOSIS. T. G. BOONACKER, Maandschr. v. kindergeneesk. **17**:45, 1949.

Three children were born to a mother of blood group OR_1 and a father of blood group AR_1. The first child became jaundiced on the fifth day of life, presented purpura of the skin and died the next day. The second child had slight jaundice on the fourth day of life, some purpura and splenomegaly. The liver increased rapidly in size, and became firm in the third week of life; the abdomen was distended and the child started to vomit and died after having vomited blood during the last day. Postmortem examination revealed a serious periportal cirrhosis of the liver. This child had blood group A and was Rh positive; the results of the Coombs test were negative.

There was no anemia or thrombocytopenia; the prothrombin time had always been markedly increased. The third child had a large liver and spleen immediately after birth and became very icteric. It also belonged to blood group AR_1. In the maternal serum no Rh antibodies were present. The titer of α-antibodies was 1:1024. This is not very high, but in the serum of the child the titer of the same antibodies was 1:128 and with the child's own erythrocytes, 1:32. The results of the Coombs test were negative. Exsanguination transfusion was performed with OR_1 blood from which the α and β antibodies had been removed. The child remained well, the icterus disappeared after one week and the child recovered.

The question is posed whether or not these children actually suffered from hemolytic disease of the newborn, due to A-O antagonism, and whether or not liver cirrhosis of the second child was due to an antigen-antibody reaction in the liver or due to chronic hemolysis.

VAN CREVELD, Amsterdam, Netherlands.

THE ROLE OF THE PLACENTA AND OTHER ORGANS IN A HEMOLYSIS FROM RHESUS ANTAGONISM. J. H. VAN BOLHUIS, Maandschr. v. kindergeneesk. **17**:99, 1949.

On the basis of serologic investigations in 186 placentas, the author defends the view that in certain infants the placenta contains Rhesus antigens and that the mother is sensitized by the antigens, present in the trophoblast, which enter into her circulation.

The placentas of Rhesus-positive infants suffering from hemolytic disease of the newborn caused by a Rhesus incompatibility nearly always exercise an inhibiting effect on Rhesus agglutinins. This influence was demonstrated in 31 out of 36 placentas examined.

The placentas of 28 Rhesus-negative infants appeared not to have this effect. On examining 122 placentas of healthy Rhesus-positive infants, in 16 an inhibition of Rhesus agglutinins after contact with placenta suspensions could be noted.

In view of the serologic findings it must be accepted that in only a limited number of Rhesus-positive persons the placenta contains Rhesus antigens. This explains why only about 5 per cent of the Rhesus-negative women married to Rhesus-positive men have children suffering from the hemolytic disease of the newborn, an observation which cannot be explained by the fact that only about 50 per cent of the Rhesus-negative persons can produce Rhesus antibodies.

On account of theoretical considerations van Bolhuis is of the opinion that not all placentas of siblings of whom the father is homozygous Rhesus positive need contain Rhesus antigens. Clinical experience seems to confirm this view.

In view of the correlation found in the inhibiting effect of placenta and tissues in one and the same person toward Rhesus agglutinins, it is being considered if in this way at least a part of the benign cases of hemolytic disease (congenital anemia) can be explained.

FROM THE AUTHOR'S SUMMARY.

Acute Contagious Diseases

POLIOMYELITIS: III. BULBAR POLIOMYELITIS: A STUDY OF MEDULLARY FUNCTIONS. A. B. BAKER, HOWARD A. MATZKE and JOE R. BROWN, Arch. Neurol. & Psychiat. **63**:259 (Feb.) 1950.

Detailed histological studies of the medulla were done in 80 cases, and the pathological conditions observed were correlated with the clinical symptoms. On this basis it is possible to divide bulbar poliomyelitis into four symptomatic types: involvement of the nucleus ambiguus, resulting in dysphagia and dysarthria; involvement of the small reticular cells, governing respiration; involvement of the large reticular cells regulating circulation, and damage to both large and small reticular cells.

MCGUIGAN, Evanston, Ill.

THE MOLE AS A POSSIBLE RESERVOIR OF POLIOMYELITIS. L. E. RECTOR, Arch. Path. **47**:366 (April) 1949.

Rector hypothesizes that the mole may be the natural reservoir of poliomyelitis for the following reasons: 1. It is found throughout the temperate and tropical zones. 2. Its distribution may account for the frequently observed tendency of the disease to start and have a higher

incidence in rural than urban populations. 3. Its habits of coming out on the surface of the ground during the hot summer months in search of worms and water may account for the seasonal tendency of the disease in man. Also, in the winter its runs are deep in the earth, but in the summer the runs are so shallow that they are barely covered with the roots of overlying vegetation. Contact with the virus may be made by persons lying on infected ground. In the city this should take place in parks where the mole is to be found. 4. The mole has been so inconspicuous as to have escaped notice to date.

To test his theory, the author took 43 moles from Forest Park in St. Louis and exposed them to or inoculated them with the virus of poliomyelitis taken from different sources. Only two animals survived. A number of them developed symptoms suggestive of damage to the central nervous system. These symptoms included lethargy, paralysis of limbs, excitability and urinary incontinence. Anorexia and cardiac arrhythmias were also observed. No lesions, however, which were typical of poliomyelitis were found at autopsy, but the author feels that this is not unique since similar negative findings having been reported by other investigators in other animals dying with the disease.

On the other hand, successful passage of the virus was made from mole to mole and from mole to Swiss mouse and cotton rat. Attempts to pass the virus to three monkeys were unsuccessful. The author feels that his experiments bring out two facts: first, that cross infection between moles in casual contamination is apparent, and, second, that the frequently encountered long survival times of some of the animals facilitate the subterranean harboring of the disease in epizootic form between epidemics in human beings. If the hypothesis is proved valid, there may be found a fair explanation as to why poliomyelitis is higher in males than in females, for "little boys are much more likely to be playing in dirt than are little girls."

HAW CHAN, San Francisco.

BILATERAL OPTIC NEURITIS FOLLOWING CHICKEN POX. HARVEY A. HATCH, J. Pediat. **34**:758 (June) 1949.

Two weeks after the onset of varicella in a 5 year old child, bilateral optic neuritis developed, with marked impairment of vison. Six weeks later the child had recovered almost completely.

MACDONALD, Pittsburgh.

LABORATORY STUDIES OF CEREBROSPINAL FLUID IN MENINGITIS AND POLIOMYELITIS. HAROLD H. JOFFE AND ARTHUR H. WELLS, Minnesota Med. **32**:608 (June) 1949.

Joffe and Wells attempt to determine the diagnostic value of certain common laboratory procedures. They state that a total cell count of over 2,000 per cubic millimeter is almost certainly caused by one of the bacteria other than the tubercle bacillus. Rarely, these other bacteria may give rise to a meningitis in the early stages of which the total count is less than 100. A differential count with more than 15 per cent lymphocytes greatly indicates inflammations due to the tubercle bacillus or the poliomyelitis virus. In these two groups seldom is there fewer lymphocytes, but the acute suppurative meningitides cases occasionally do have more than 15 per cent lymphocytes. In the latter the total count would in the great majority of cases be over 2,000 per cubic millimeter.

Quantitative protein determinations may be of some value in differentiating poliomyelitis from the other two causes of meningitis but must be interpreted with care in the cases of meningitis in the early stage. The low chloride content of spinal fluid is of distinct differential value in distinguishing tuberculous meningitis from poliomyelitis. A level below 600 is almost certainly the result of the former. Tuberculous meningitis can be differentiated with fair certainty from poliomyelitis by the occurrence of an almost uniformly low level of spinal fluid sugars in the former as compared with a level above 50 mg. per 100 cc. in the latter.

STOESSER, Minneapolis.

IMMUNIZATION IN PRACTICE. G. M. LITTLE, Canad. M. A. J. **62**:254 (March) 1950.

Little recommends routine immunization to the extent that he suggests payment for the service by the public health authorities. Immunizations against whooping cough, diphtheria,

tetanus and smallpox are considered essential, whereas typhoid and scarlet fever vaccines are desirable.

McGUIGAN, Evanston, Ill.

TREATMENT OF WHOOPING COUGH. S. K. ROY, Indian J. Pediat. **17**:20 (Jan.) 1950.

General measures in treatment are discussed. Aerosporin® (polymixin B) and streptomycin are mentioned as offering promise but remaining to be evaluated.

McGUIGAN, Evanston, Ill.

DICK TEST IN EGYPTIAN CHILDREN: RESULTS OF 5,291 TESTS. M. DIWANY and S. AWWAAD, J. Roy. Egyptian M. A. **33**:20, 1950.

Dick tests were done on 5,291 children between the ages of 2 and 15 years. Percentages of positive reactions varied from 3.7 in the older age groups to 27.4 in the younger ages. The evidence indicates a greater immunity in Egyptian children than in children of other nationalities.

McGUIGAN, Evanston, Ill.

RUBELLA OR GERMAN MEASLES. IHSAN DOGRAMACI, Ann. pædiat. **173**:85 (Aug.) 1949.

The history of rubella is briefly discussed and the confusion in terminology is pointed out. The literature on the congenital malformation causing the infection during pregnancy is summarized.

The first cases seen in Turkey in which maternal rubella during pregnancy was followed by the birth of abnormal offspring are reported.

FROM THE AUTHOR'S SUMMARY.

GERMAN MEASLES IN PREGNANCY AS A CAUSE OF CONGENITAL ANOMALIES. ANDERS HAGSTRÖMER, Svenska läk.-tidning. **44**:1592 (Aug. 1) 1947.

A baby girl, birth weight, 2,340 Gm., had congenital malformation of the heart (patent ductus Botallo), deafness and mental retardation. The 21 year old mother had had German measles diagnosed by an experienced physician some time between the fifth and the seventh weeks of pregnancy.

WALLGREN, Stockholm, Sweden.

ENCEPHALITIS AFTER MEASLES AND RUBELLA. SVEN DAHL, Ugesk. f. læger **109**:151 (Feb. 6) 1947.

A report is given of a boy of 11 who showed signs of encephalitis 1½ days after the manifestation of measles exanthem. He was healthy after three months' illness. Six months later he contracted rubella and had two epileptic seizures of the jacksonian type at the height of the fever period. Later on there was slight mental retardation.

WALLGREN, Stockholm, Sweden.

RECURRENT AND CORNEOSCLERAL VARICELLA. G. M. H. VEENEKLAAS, Maandschr. v. kindergeneesk. **17**:18, 1949.

Chickenpox, running an unusual course, occurred in three children of one family. The youngest child, 7 months old, contracted chickenpox, while the older children, respectively 2½ and 5 years old, remained unaffected, although they had not had the disease previously. The youngest child was vaccinated against smallpox two months afterwards, two vaccinia lesions resulting, and four days after that chickenpox efflorescences recurred, lasting only a few days. The oldest child contracted chickenpox six days after the youngest child, the second child three weeks later. Both children had presented a vesicle on the cornea of the right eye. It is possible that the youngest and the oldest child were infected simultaneously, the incubation period being shorter in the youngest because of the previous varicella episode. This unusual fact may have been due to a temporarily lowered resistance at the time of vaccination against smallpox.

VAN CREVELD, Amsterdam, Netherlands.

ENCEPHALOMENINGITIS ACCOMPANYING RUBELLA. P. R. DAGNELIE, Nederl. tijdschr. v. geneesk. **91**:938 (April 19) 1947.

While suffering from rubella (exanthem, swelling of the lymph nodes, slight elevation of temperature, leukopenia) a young woman became somnolent and showed retardation of psychical reactions, hypersensibility and patellar and ankle clonus. No pathological reflexes were noted. There was slight stiffness of the neck. The spinal fluid was clear and colorless and contained 120 cells per 3 cubic millimeters, chiefly lymphocytes. The albumin and blood sugar levels were normal. The affection of the central nervous system appeared at the same time as the exanthem. During convalescence, after a lumbar puncture, the patient had a recurrence of the neurological and psychical symptoms, but complete recovery followed.

VAN CREVELD, Amsterdam, Netherlands.

CONGENITAL ANOMALIES AFTER RUBELLA DURING PREGNANCY. G. A. FEHMERS and C. MESDAG, Nederl. tijdschr. v. geneesk. **91**:2419 (Aug. 30) 1947.

In four children whose mothers had suffered from rubella during pregnancy the following abnormalities were found: temporary clouding of the cornea, congenital heart defect, thrombopenic hemorrhages and congenital heart defect with thrombopenic hemorrhages.

In the literature are described cataract, microphthalmia, congenital heart defects, feeblemindedness, deaf and dumbness and microcephalia.

Four points are discussed: 1. As yet it has not been proved that rubella occurred more frequently during the pregnancy of mothers of children with congenital anomalies than during the pregnancy of mothers of normal children. 2. It is a question whether the anomalies are the result of a toxic action or of a disturbance of the normal physiological state. 3. The low values of the serum globulin during fetal life explain the more serious course of infectious diseases in the fetus. 4. Finally, Fehmers and Mesdag discuss the problem of a barrier made by the placenta after the third or fourth month of pregnancy.

VAN CREVELD, Amsterdam, Netherlands.

COMPLICATIONS AFTER VACCINATION AGAINST SMALLPOX. A. W. VEGTER, Nederl. tijdschr. v. geneesk. **93**:1345 (April 23) 1949.

It is well known that children with eczema must not be vaccinated. This also holds true for healthy children who could possibly be in contact with other children known to have eczema. Vegter reports one case with fatal outcome of vaccination of a boy 2½ years old who became infected with eczema by his younger brother. A case of rubelliform eruption 11 days after vaccination is also reported. Vaccination should be performed by the family physician and must not be a mass procedure.

VAN CREVELD, Amsterdam, Netherlands.

ENCEPHALITIS POSTVACCINALIS. E. GORTER, Nederl. tijdschr. v. geneesk. **93**:1483 (May 7) 1949.

In a comment on postvaccinal encephalitis Gorter reports the case of a girl of 6 years in whom, 14 days after the first vaccination against smallpox, headache, stiff neck, fever, convulsions and coma developed. The pressure of the cerebrospinal fluid reached 22 cm. of water. The Pandy test gave a positive reaction, and the number of cells reached 200 per 3 cubic millimeters. Bacteriologic examination of the fluid showed no abnormalities. Transfusions were given with use of blood of the mother and hyperimmune serum, 8 ml. given intrathecally. Hyperpyrexia developed (42.1 C., 107.6 F.), and the patient died 24 hours later. An autopsy was not permitted.

Related conditions, such as convulsions owing to fever, are discussed, and the following directives for vaccination are recommended: Vaccinate all children between 3 and 12 months of age, with exception of those who have once shown convulsions or other signs of cerebral inferiority. Do not vaccinate in large groups and not when other forms of encephalomeningitis are more frequent.

VAN CREVELD, Amsterdam, Netherlands.

Acute Infectious Diseases

A Serologic and Clinical Study to Estimate the Frequency of Toxoplasmosis in Italy. P. Tolentino and A. Razzi, Minerva pediat. **1**:63 (Feb.) 1949.

The Sabin neutralization test with use of rabbits, which is used for the diagnosis of toxoplasmosis, was done in 71 cases in northern Italy. The subjects included children suspected of having had toxoplasmosis and parents of such children, also all patients with neurological disease seen at the children's clinic in Genoa and certain adults whose symptoms suggested the toxoplasmosis. Seventeen positive reactions were obtained; 9 were for children whose condition suggested a positive clinical diagnosis of toxoplasmosis, 6 for parents of such children and 2 for children with tuberculous meningitis. The reaction for one mother was positive although it was negative for her encephalopathic child. The occurrence of the two positive reactions for children with tuberculous meningitis raises some doubt as to the absolute specificity of the test.

Higgins, Boston.

A New Case of Toxoplasmosis. P. Tolentino, Minerva pediat. **1**:101 (March) 1949.

A child of 8 years showed focal convulsions of the left arm and leg, left hemiparesis and hypertonia, spots of atrophic chorioretinitis, intracerebral areas of calcification and a deformity of the right lateral ventricle revealed by pneumoencephalography. The symptoms were first noticed when the child was under 6 months of age. In view of the symptomatology and a positive Sabin neutralization reaction, a diagnosis of toxoplasmosis was made.

Higgins, Boston.

Brahme's Formula and the Prognosis in Rheumatic Fever of the Child. G. Poli, Minerva pediat. **1**:125 (April) 1949.

Brahme has presented a formula to serve as one guide in determining a suitable time for the rheumatic patient to cease being a bed patient; Brahme's patients were all adults (*Acta med. Scandinav.* **88**:565, 1936). Poli applies a somewhat modified formula in the cases of 20 children with rheumatic fever. The formula involves a mathematical comparison of the blood sedimentation rates taken at one week intervals. Pinto regards the formula of value in making a decision as to when a child with rheumatic fever may be up and about when considered with other clinical and laboratory observations.

Higgins, Boston.

Clinical-Statistical Studies of 113 Cases of Rheumatic Fever Observed Among Convalescents in the Clinic from 1926 to 1946. Armando Carnevale, Pediatria **55**:413, 1947.

From a statistical-clinical study on 113 cases of rheumatic disease, observed in the Pediatric Clinic of Naples from 1926 to 1946, it appears that the highest frequency for the articular manifestations is reached between the eighth and tenth year of age, and for the chorea syndrome, at the beginning of adolescence (12 years).

The author observed also that the younger the child is the greater is the tendency for the relapses to repeat the characters of the initial polyarticular manifestations, whereas at the age at which chorea is more frequent, the relapses tend to assume the choreic form, so that this can suggest an etiopathogenetic connection between chorea and rheumatic infection.

Among the author's cases the apparently primary cardiopathic cases appear in a low percentage, whereas almost all the cases with polyarticular manifestations seem to be complicated, either at the first attack or during the relapses, by cardiac injuries.

Children affected with polyarthritis show cardiac injuries more frequently than do those affected with chorea.

From the Author's Summary.

Prophylactic Typhoid-Paratyphoid Vaccination Intradermally in Children. S. Viridis, Pediatria **57**:531 (July) 1949.

Thirty infants (9 and 10 months old) were given three injections of a typhoid-paratyphoid vaccine intradermally at 10 day intervals. There were no local or generalized reactions. The

agglutinins appeared in the blood serum quite as readily as in the serum of controls receiving the vaccine by hypodermic injections.

HIGGINS, Boston.

TREATMENT OF TETANUS IN CHILDHOOD. SEVERINO PEDONE, Riv. clin. pediat. **46**:803 (Dec.) 1948.

In 28 cases of tetanus, five of which were in newborn infants, the treatment consisted in intensive serum therapy, with serum given fractionally; generous doses of phenobarbital derivatives; special care of the patients, and all possible forms of symptomatic and general therapy. Of the 28 patients, 21 were cured (75 per cent of the total); of the five newborn infants, three were cured and two died. With the systematic employment of the customary antitetanus therapy, the prognosis of this disease, which was once so serious in the field of pediatrics, tends toward notable improvement.

FROM THE AUTHOR'S SUMMARY.

A STUDY OF THE HEMORRHAGIC DIATHESIS IN THE INFECTIOUS DISEASES OF CHILDREN. J. COLOMINAS PUIG and J. CABEZAS VASQUEZ, Acta pediat. españ. **85**:22 (Jan.) 1950.

The authors review the mechanism of coagulation of the blood and take up the relation of the various factors and the chemistry of each for 50 children with various illnesses, such as measles, pertussis, meningitis, diphtheria, typhoid, tetanus and pneumonia. These children were kept under observation for a month. Blood studies were done immediately on their entrance into the Municipal Hospital for Infectious Diseases at Barcelona. These were repeated every other day, and on leaving the hospital the patients were watched for a period of one month through the outpatient department, and blood studies were continued.

The following determinations were made: (1) coagulation time; (2) bleeding time; (3) clot retraction; (4) prothrombin time; (5) blood vitamin C; (6) urine vitamin C; (7) thrombocyte (platelet) count; (8) Rumpel-Leede sign; (9) fibrinogen determination.

In none of the cases was there a frank hemorrhagic diathesis. In five cases there were mild evidences of hemorrhagic symptoms, such as bleeding gums, epistaxis, ecchymosis in the eyelids and eyes and purpura-like lesions in the skin. These disappeared at the end of the illness in most cases without vitamin or coagulation therapy. In only one case of pertussis was the hemorrhagic complex prolonged. After treatment with vitamin C and K these hemorrhagic symptoms disappeared.

The laboratory examinations showed that 42 per cent had one or more alterations in the substances which work together to cause coagulation. Changes in the following were among the most frequent changes which occurred: thrombocytes (platelets), prothrombin time, clot retraction, bleeding time and vitamin C level. Twenty-eight per cent had two abnormalities; 16 per cent had three deficiencies; and 14 per cent had four deficiencies. The thrombocytes (platelets) showed the most frequent changes both in function and in morphology.

Such studies may point the way to prophylactic measures against childhood infections which may be used when the hemorrhagic diathesis is considered to be present although subclinical.

ALLEN, Santa Fe, N. Mex.

A CASE OF CONGENITAL MALARIA OCCURRING SEVEN DAYS AFTER ELECTIVE CESAREAN SECTION. HUEI-LAN CHUNG, K. T. LIM, AN CHANG, W. P. WANG and Z. S. KOEH, Chinese M. J. **66**:449 (Aug.) 1948.

The mother of an infant with malaria had been given a blood transfusion 11 days before the delivery. It was discovered later that the donor had malaria. The day after delivery by cesarean section chills and fever developed in the mother. Four days later Plasmodium vivax was recovered from her blood. The infant had an irregular low fever at the age of 7 days, and at the age of 18 days P. vivax was recovered from his blood. Both mother and child recovered.

MACDONALD, Pittsburgh.

FEBRIS CANICOLARIS, A RARE ZOONOSIS? J. E. MINKENHOF, Nederl. tijdschr. v. geneesk. **91**: 1938 (July 19) 1947.

In the Institute of Tropical Hygiene in Amsterdam, 40 cases of canicola fever have been observed since 1933, and in 1946 there were 10 cases within three months. Hence, probably the disease is not so rare as is generally accepted.

The disease is caused by Leptospira canicola, which is found only in men and dogs. Many dogs are infected and excrete Leptospira in the urine. The symptoms of the disease in men are acute onset, headache, vomiting, pain in the muscles (not only in the calves) and often increased irritability and disturbances of consciousness. All patients in the clinic showed symptoms of meningeal irritation nine to 15 days after the beginning of the disease, with the result that the diagnosis at admission often was meningitis or poliomyelitis. The number of cells varied from 12 to 2,450 per 3 cubic millimeters; preponderance of the granulated leukocytes occurred as often as that of the lymphocytes. The urea content was always increased (600 to 1,400 milligrams per liter). In six cases icterus was present; one case was fatal.

VAN CREVELD, Amsterdam, Netherlands.

Chronic Infectious Diseases

THE CELLULAR TRANSFER OF CUTANEOUS HYPERSENSITIVITY TO TUBERCULIN IN MAN. H. SHERWOOD LAWRENCE, Proc. Soc. Exper. Biol. & Med. **71**:516 (Aug.) 1949.

Chase (*Proc. Soc. Exper. Biol. & Med.* **59**:134, 1945) demonstrated the transfer of specific cutaneous hypersensitivity of the "delayed type" by injection into unsensitized guinea pigs of leukocytes which were isolated from peritoneal exudates produced in sensitized guinea pigs. The method of Minor and Burnett (*Blood* **7**:799, 1948) was used by Lawrence in isolating viable leukocytes from human blood. In 12 consecutive instances it has been possible by passive transfer to cause positive cutaneous reactions in human recipients with tuberculin-negative reactions by the injection of viable leukocytes obtained from the blood of persons with tuberculin-positive reactions. Transfer of similarly prepared leukocytes from the blood of persons with tuberculin-negative reactions did not cause positive reactions. This cutaneous hypersensitivity to tuberculin persisted from four days to three months and could be produced again in the same person. The degree of induced hypersensitivity to tuberculin seemed to be related to the dosage of leukocytes used and the degree of tuberculin hypersensitivity of the leukocyte donor.

HANSEN, Galveston, Texas.

PARAAMINOSALICYLIC ACID (PAS): THERAPY OF TUBERCULOSIS. J. LEITNER and P. MASSON, Schweiz. med. Wchnschr. **80**:375 (April 15) 1950.

The effect of treatment of various forms of tuberculosis in humans by means of paraaminosalicylic acid (PAS) is discussed rather fully. The drug was given by mouth.

AMBERG, Rochester, Minn.

PROPORTION OF THE BLOOD FATTY ACIDS, SATURATED AND UNSATURATED, IN CHILDREN WITH DIVERSE TUBERCULOUS LOCALIZATIONS. GIOVANNI BOI, Ann. ital di pediat. **3**:148 (April) 1950.

Boi examined the proceedings of fatty acids of blood and their modification by means of streptomycin in the various children's tuberculous syndromes.

Generally normal equilibrium is interrupted in these syndromes because of the reduction of unsaturated fatty acids; however, the total number of acids and the saturated acids generally appear increased.

Generally the streptomycin administration determines a reduction of the total fatty and saturated acids and an almost constant increase of unsaturated acids and of the "unsaturation index" in different degrees for various subjects, independently of the doses of antibiotic employed.

Boi attributes these various aspects of metabolism of fatty acids to the function of the hepatic cells, the action of tuberculous poison and the action of antibiosis as an antitoxin and as an equilibrator of processes of oxidation.

FROM THE AUTHOR'S SUMMARY.

EFFECT OF STREPTOMYCIN ON ELIMINATION OF VITAMIN B_2 IN URINE. L. SALMI and L. MANTONI, Clin. pediat. **32**:17 (Jan.) 1950.

Two groups, one of 10 normal children and one of 10 children with tuberculous meningitis, were studied. The daily elimination of riboflavin in the urine was found to be about twice as high in the tuberculous children (91 micrograms per 100 cc.) as in the normal children (42 micrograms per 100 cc.). When 20 mg of riboflavin was given parenterally, the rate of excretion was found to be higher in the tuberculous children. When streptomycin was given to each group, the injection of riboflavin resulted in a more rapid excretion of the vitamin in the normal than in the tuberculous group. Streptomycin therapy seemed to favor the retention of the vitamin B_2 by the tuberculous child.

HIGGINS, Boston.

DOES PENICILLIN CAUSE COMPLICATIONS IN CHILDREN WITH TUBERCULOUS CONDITIONS? P. ROMUALDI, Pediatria **58**:21 (Jan.) 1950.

The appearance of tuberculous abscesses was observed in several children shortly after they had been treated with penicillin for pyogenic infections.

HIGGINS, Boston.

AN INDEX OF ALLERGY TO TUBERCULIN. F. COPELLO and S. CONTE, Pediatria **58**:44 (Jan.) 1950.

The index R/S is recommended as indicating the degree of allergy to tuberculin. S is the arithmetical average erythematous area calculated from measurements made every 24 hours up to the maximum reaction time (usually 48 hours); R is the arithmetical average erythematous area on the next three days. Purified tuberculin (1 to 1,000 strength) is recommended, and no preliminary tests should have been made. Only one injection at a time should be given.

HIGGINS, Boston.

SIX CASES OF TUBERCULOUS MENINGITIS, TREATED WITH STREPTOMYCIN AND SULFONE. G. BONONI, Policlin. inf. **16**:645 (Dec.) 1948.

Although the streptomycin treatment of tuberculous meningitis has been one of the most glorious conquests of medicine, it must be remembered that not all patients are completely cured and that fatal relapses may occur after seeming cures.

HIGGINS, Boston.

SPECIFIC DIAGNOSIS OF TUBERCULOSIS BY INTRACUTANEOUS ADMINISTRATION OF TEBEPROTEIN. E. TOENNIESSEN, Med. Klin. **45**:560 (May 5) 1950.

Purified tuberculins, like the old tuberculin, are obtained from culture fluid of the tubercle bacillus. Tebeprotein is prepared by alkali extraction of the tubercle bacilli. It contains two proteins: one has a molecular weight of 100,000 to 150,000 (from sedimentation constant); the other has a molecular weight of about 35,000. The preparation is handled by means of the balance. It is used in dilutions of which 0.1 ml. contains 1/1,000 mg. or 1/10,000 mg. It is recommended that the two dilutions be administered simultaneously and the result read after 48 hours. When the lower concentration produces a reaction, a fresh active process is highly probable. Less active processes react only to the stronger concentration, and inactive processes react only weakly to the stronger concentration and not at all to the higher dilution.

AMBERG, Rochester, Minn.

RESULTS OF THE COMBINED TREATMENT OF MENINGITIS TUBERCULOSA WITH STREPTOMYCIN AND PARAAMINOSALICYLIC ACID (PAS) COMPARED WITH THE TREATMENT BY STREPTOMYCIN ALONE. W. LOEFFLER and S. MOESCHLIN, Schweiz. med. Wchnschr. **80**:365 (April 15) 1950.

Since of 17 patients suffering from tuberculous meningitis treated with streptomycin only three survived two to three years, a combined treatment with paraaminosalicylic acid (PAS)

was given to nine adults. Of these eight are still alive after seven to 11 months, apparently clinically cured.

It seems important that the combined treatment is started as early as possible. Dihydrostreptomycin is given intramuscularly and streptomycin, intraspinally. PAS is given, in a dosage of 30 to 40 Gm. daily, by intravenous drop infusion. The treatment is outlined in detail.

AMBERG, Rochester, Minn.

Diseases of Blood, Heart and Blood Vessels and Spleen

A CASE OF TETRALOGY OF FALLOT WITH RIGHT AORTIC ARCH AND AN ATRESIA OF THE VENOUS BRACHIOCEPHALIC TRUNK. E. ROSSI and M. ROHNER, Helvet. paediat. acta **3**:481 (Dec.) 1948.

Rossi and Rohner give a description of a rare case of tetralogy of Fallot with right aortic arch associated with stenosis of the left innominate vein. These malformations occurred in a 12 year old girl, who died during the course of an operation.

FROM THE AUTHORS' SUMMARY.

THE ACTION OF THIOURACIL ON THE COAGULATION OF THE BLOOD. L. A. PALOS and J. KOMAROMY, Schweiz. med. Wchnschr. **78**:1130 (Nov. 20) 1948.

Experiments carried out on rabbits showed that large doses of thiouracil given over long periods decrease the thrombin-inactivating power of the blood and so increase its coagulability.

AMBERG, Rochester, Minn.

REPORT OF AN ATYPICAL CASE OF HEMOLYTIC ANEMIA WITH SPLENOMEGALY. M. ORLANDELLI, Clin. pediat. **30**:359 (June) 1948.

In a girl of 2½ years an acute hemolytic anemia with marked jaundice suddenly developed. The girl died 47 days after the condition was first recognized. There were anisocytosis, poikilocytosis and hypochromia of the red blood cells; the fragility of the red blood cells was normal. There were marked splenomegaly and a moderate degree of hepatomegaly. Histological examination of the liver and the spleen showed heterotopic islands of hemopoiesis.

HIGGINS, Boston.

THE TECHNIQUE AND DIAGNOSTIC VALUE OF THE PRECORDIAL LEAD IN ELECTROCARDIOGRAPHY. L. SALMI, Clin. pediat. **30**:385 (June) 1948.

The characteristics of the electrocardiograms of healthy and ill children when the precordial lead is used are discussed.

HIGGINS, Boston.

ACUTE PRIMARY MYOCARDITIS WITH LESIONS INVOLVING THE PAPILLARY MUSCLES OF THE MITRAL VALVE IN A CHILD WITH AN ENLARGED THYMUS GLAND. M. A. DINA, Clin. pediat. **30**:477 (Aug.) 1948.

In a seemingly healthy girl of 13 months on the third day of an acute grippal infection cardiac failure developed. The patient died, and autopsy revealed an enlarged thymus (weight, 30 Gm.); an enlarged heart, especially on the left side; myocardial involvement of the mitral papillary muscles with lysis of the muscle cells and calcareous deposits, and a terminal bronchopneumonia. There was some coronary arteritis. An allergic cause is suggested.

HIGGINS, Boston.

CHANGES IN THE CARDIAC VOLUME AFTER DIGITALIS THERAPY. DONATELLA GIAVANETTI, Clin. pediat. **31**:44 (Jan.) 1949.

The conclusion is drawn that the action of digitalis on the heart rate and volume is through the neurovegetative system, which in children shows a vagal predominance. Lanatoside C has proved efficacious, even for a prolonged digitalis effect.

HIGGINS, Boston.

GAUCHER'S DISEASE IN A TWO YEAR OLD GIRL. LAURA ANTI, Lattante **18**:356 (June) 1947.

The diagnosis of Gaucher's disease in this case was confirmed by histological examination of material obtained by splenic puncture.

HIGGINS, Boston.

IN VITRO OBSERVATIONS ON THE LIFE SPAN OF LEUCOCYTES GIVEN IN A TRANSFUSION. LAURA LANDUCCI, Lattante **18**:360 (June) 1947.

White blood cell counts were made on citrated blood. The blood was mixed with dilutions of blood serum in proportions of 1:1, 1:2, 1:3 and 1:5. Further blood counts were made on these mixtures at intervals of 10 minutes for one hour. The number of white blood cells had diminished by 50 per cent in the 1:1 dilution and considerably more in the weaker dilutions after a period of one hour.

HIGGINS, Boston.

THE BLOOD PICTURE IN THE PARENTS OF A PATIENT WITH COOLEY'S ANEMIA. LAURA MELE, Lattante **19**:520 (Sept.) 1948.

There were alterations in the blood of both parents of a child with typical familial erythroblastic (Cooley's) anemia. The mother's blood examination revealed anemia, microcythemia, hypochromia and decreased fragility of the red cells. Examination of the father's blood revealed anemia, anisocytosis, poikilocytosis, ovalocytosis, hypochromia, nucleated red cells and decreased fragility of the red cells.

HIGGINS, Boston.

LYSOZYME CONTENT IN THE BLOOD SERUM OF CHILDREN OF DIFFERENT AGES. G. MAINI and F. SOZZI, Lattante **20**:9 (Jan.) 1949.

The bacteriolytic potency of the serums of children of various ages was tested against Micrococcus lysodeikticus. There was little difference in the potencies (lysozyme content) of the serums of premature infants, artificially fed infants and older children. However, in the serums of breast-fed infants the content was lower.

HIGGINS, Boston.

A CLINICAL-MEDULLARY REMISSION IN ACUTE LEUKEMIA. E. CIFARELLI, Lattante **20**:20 (Jan.) 1949.

In February a 5 year old boy was found to have acute leukemia with total metaplasia in a bone marrow smear. In late March a severe case of pertussis and bronchopneumonia developed. Death appeared imminent. Treatment was intensive and by transfusions, penicillin and urethan. After 10 days the child was no longer acutely ill from the pertussis. The blood counts and smears from the blood and bone marrow were normal. This remission of the leukemia lasted only 40 days. Then the symptoms and the hematologic findings of leukemia returned. Urethan proved of no therapeutic value. The child died in July.

HIGGINS, Boston.

THE PROPORTION OF GLOBULIN CHLORINE TO PLASMA CHLORINE. MARIO SAGGESE, Pediatria **55**:445, 1947.

The author draws attention to the importance of the hematocrit value in testing for blood chlorine. He proposes a simple formula by which the hematocrit value is derived from the data of total plasmatic and globular chloremia.

FROM THE AUTHOR'S SUMMARY.

HISTOLOGICAL FINDINGS IN THE PLACENTA OF A MOTHER, WHOSE CHILDREN HAD COOLEY'S ANEMIA. G. SANSONE and M. FERABOLI, Policlinico inf. **16**:373 (Aug.) 1948.

A mother had had two children with familial erythroblastic (Cooley's) anemia; the third child, although still apparently normal at the age of 6 months, carried some latent stigmas of that condition, namely, enlarged liver, enlarged spleen, icterus neonatorum of 10 days' duration and a red blood cell count of 3,290,000, without erythroblastosis. The mother was Rh negative but demonstrated no abnormal agglutinins in her serum.

The placenta of the third child was examined histologically. There were extensive vascular proliferation, hyperemia, increased size of the villi, decreased intervillar spaces and absence of Langhans cells. There was no evidence of syncytial proliferation; numerous vessels below the syncytium were in direct contact with the intervillous spaces and consequentially with the maternal blood. At several places diapedesis was observed.

HIGGINS, Boston.

Nervous Diseases

THE NEUROLOGIC DEFICIT ASSOCIATED WITH LIPOMAS OF THE CAUDA EQUINA. ROBERT C. BASSETT, Ann. Surg. **131**:109 (Jan.) 1950.

Congenital lipomas of the lumbosacral region may produce serious neurological deficits, such as a profound peripheral neuropathy, trophic ulcers, disturbances of bowel and bladder function and irreversible skeletal changes, if not treated early in life.

The diagnosis is obvious with the combined picture of the soft but not fluctuant mass situated in or near the midline and covered with healthy skin and associated bifid deformity of the lumbosacral spine.

Treatment is surgical, the optimum time being during the first three or four months of life.

BANTIN, Omaha.

THE USE OF PHENURONE IN THE TREATMENT OF EPILEPSY. SAMUEL LIVINGSTON and LASLO KAJLI, J. Pediat. **36**:159 (Feb.) 1950.

Of 104 epileptic patients treated with phenacetylurea (phenurone®), 45 were either greatly improved or completely controlled. Side reactions, the most distressing of which were personality changes, occurred in 28 per cent of the patients.

MACDONALD, Pittsburgh.

COLLECTIONS OF SUBDURAL FLUID COMPLICATING MENINGITIS DUE TO HAEMOPHILUS INFLUENZAE (TYPE B). R. JAMES MCKAY JR., RUSSELL A. MORISSETTE, FRANC D. INGRAHAM and DONALD D. MATSON, New England J. Med. **242**:20 (Jan. 5) 1950.

Nine cases of a syndrome of collections of subdural fluid with high protein content occurring among 23 cases of meningitis due to Hemophilus influenzae seen during a six month period are the subject of this preliminary report. The majority of cases occurred in infants under 1 year of age. The fluid was encapsulated in seven patients. The clinical symptoms, prognostic implications and therapy of the condition, namely, repeated subdural taps, bilateral temporal burr holes to attempt to rule out the presence of inner and outer subdural membranes and subsequent craniotomies to remove any such membrane located, are similar to those of chronic subdural hematoma in infants and children. The indications for subdural taps are outlined as (1) general clinical impression, (2) presence of fever after 48 to 72 hours of treatment, (3) cultures positive for H. influenzae after 48 hours of treatment, (4) convulsions after subsidence of infection, (5) focal convulsions at any time, (6) vomiting after apparent subsidence of infection and (7) appearance of any gross neurological abnormality during the immediate convalescence period.

It is believed that early recognition and treatment of this complication may effect a reduction in the incidence of residual cerebral damage in patients with meningitis caused by H. influenzae.

WHEELOCK, DENVER.

GEMONAL® (5, 5-DIETHYL 1-METHYL BARBITURIC ACID): NEW DRUG FOR CONVULSIVE AND RELATED DISORDERS. M. A. PERLSTEIN, Pediatrics **5**:448 (March) 1950.

Gemonal® (5, 5-diethyl 1-methyl barbituric acid) is a relatively new nontoxic anticonvulsant barbiturate. In a series of 50 patients with epilepsy it was found to be of practically no benefit in treatment of idiopathic forms of the disease, but it definitely improved 18 of 35 patients with seizures due to organic disease of the brain.

This property of being more effective in organic than in idiopathic epilepsy is unique among the antiepileptic drugs. Greatest benefit from the drug was noted for patients with myoclonic spells.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF HEMOPHILUS INFLUENZAE B MENINGITIS: REPORT OF 67 CASES. KATHRYN J. MCMORROW and FRANKLIN H. TOP, Pediatrics **5**:452 (March) 1950.

The authors' series consisted of 67 patients, 17 of whom died, which gave a gross fatality rate of 25.4 per cent. Almost one half of the patients were under 2 years of age, and these accounted for 65 per cent of the deaths. By disregarding data from patients who died within 36 hours after admission and patients first admitted to the hospital after 21 days of illness, the corrected fatality rate of 18.2 per cent is obtained for the group under 2 years of age.

Death occurred in four patients admitted and first treated at the end of the third week of illness. The two deaths in the group under 2 years which had received sulfadiazine, serum and streptomycin occurred in patients who had been ill three weeks before receiving treatment.

The prognosis is likely to be unfavorable for patients under 2 years of age if treatment is delayed beyond the fourteenth day.

The fatality rate for patients who received sulfadiazine and serum was the same in this series as for patients who received streptomycin in addition to these.

Serotherapy proved ineffectual for the group under 2 years of age when its use was delayed to beyond the fourteenth day of illness. With respect to prognosis, the intravenous route for administration of serum offers no advantage over the intramuscular route.

FROM THE AUTHORS' SUMMARY.

CLINICAL CORRELATES OF THE FAST AND THE SLOW SPIKE-WAVE ELECTROENCEPHALOGRAM. WILLIAM G. LENNOX and JEAN P. DAVIS, Pediatrics **5**:626 (April) 1950.

In order to test a hypothesis that slow spike and wave formations may be only the immature form of the three per second dart and dome formation of "petite absence" and to learn more about the meaning of a dysrhythmia that consists of an alteration of wave frequency, Lennox and Davis have compared the clinical histories and examinations of 400 patients, 200 from each group. The group with the slow pattern contained relatively more males; the patients were younger both when seizures began and at the time of examination; their histories contained a greater variety of seizure phenomena and their electroencephalograms were more associated abnormalities than were those of the patients in the group with the fast pattern. The evidence of brain damage that antedated seizures was much greater and the family history of epilepsy was somewhat less in the slow group as contrasted with the fast, and yet heredity played as great a part in the slow group as in a large unselected group of "genetic" epileptics. The intelligence of the slow group was lower than that of the fast group.

Slow spike-hump discharges are more diverse in configuration and distribution and oftener localized and solitary than are dart-dome discharges. The slow form is less often identified with specific clinical symptoms, though in this group of children 53 per cent had a history of one or more of the petit mal quartet. "Akinetic" falls or simple or massive myoclonic jerks may accompany solitary discharges. The last-named seizure was confined to the very young patients. Of the infants, 55 per cent had this form. Periods of sudden stillness, staring, sagging, small jerkings or mild tonicity, often without full loss of consciousness, may be the clinical correlates of serial discharges. Though the patients with the slow pattern were less responsive to trimethadione (tridione®) or other therapy than were the patients with the fast pattern, control of seizures and even of this peculiar spike-hump dysrhythmia may be possible among those with the slow pattern.

The property of alternation of wave frequency may bear a specific relation to genetic (essential) epilepsy. The slow spike and wave formation does not represent simply an immature form of the three per second dart and dome pattern but rather the confluence of three influences; extreme youth, heredity and neuropathological change.

FROM THE AUTHORS' SUMMARY.

A VIRUS ISOLATED FROM PATIENTS DIAGNOSED AS NON-PARALYTIC POLIOMYELITIS OR ASEPTIC MENINGITIS. JOSEPH L. MELNCK, ERNEST W. SHAW, and EDWARD C. CURNEN, Proc. Soc. Exper. Biol. & Med. **71**:344 (July) 1949.

During the summer and fall of 1948 there occurred an epidemic resembling nonparalytic poliomyelitis in southern New England. Samples of feces were obtained from 13 patients with

no paralytic signs and three patients with definite muscular weakness. Fecal samples from five of the nonparalytic patients produced disease in newborn mice but not in monkeys. The new virus was also found in the feces of two patients with the diagnoses of "fever of unknown origin." Samples from two patients with nonparalytic disease were shown to contain poliomyelitis virus when injected into monkeys and did not produce disease in newborn mice. In one physician engaged in this work a vague febrile illness of eight days' duration developed. Virus was recovered from the feces and nasopharyngeal washings, and neutralizing antibodies developed in increasing titer during convalescence. Extensive study of the experimental disease was made in Swiss mice and chimpanzees and in human and extrahuman sources for immunologic types. The agent is similar to that reported by Dalldorf and Sickles (*Science* **108**:61, 1948). At least two immunologic types of the virus exist. The virus was widespread in the country in 1948, judging from its isolation from sewage and flies in widely separated areas. Subclinical infection may be produced in chimpanzees by oral administration of the virus.

HANSEN, Galveston, Texas.

INTRACRANIAL SUPPURATION. JULIAN TAYLOR, Proc. Roy. Soc. Med. **43**:129 (Feb.) 1950.

A discussion of various types of suppuration, including suppurative meningitis, infectious sinus phlebitis, abscess of the brain and acute suppurative encephalitis, is presented. Several case reports are outlined. The author concludes that in most instances antibiotic and sulfonamide therapy with incision and drainage are much to be preferred over complete excision of abscesses.

HEARD, Monterey, Calif.

Psychology and Psychiatry

THE NEEDS FOR INPATIENT CARE AND TREATMENT OF MENTALLY ILL CHILDREN IN THE COMMONWEALTH OF MASSACHUSETTS. THADDEUS P. KRUSH, New England J. Med. **241**:441 (Sept. 22) 1949.

The author defines the need for psychiatric recognition and treatment of personality deviations among the younger age groups. The four prominent groups of unstable children who need inpatient care and treatment are listed: those who exhibit marked withdrawal, those who habitually run away, those who are excessively aggressive and those who are abnormally hyperactive and distractible.

The present hospital facilities provided for the psychiatric care of mentally ill children in the state of Massachusetts are described; the inadequacies of this physical setup are outlined, and a sober plea for reorganization of the situation, based on sensible and experienced suggestions for a more efficient physical plant supplemented with adequate, trained and integrated attendant, nursing, and medical personnel, is made.

S. E. WHEELOCK, Denver.

PALMAR DERMATOGLYPHICS IN MONGOLISM. HAROLD CUMMINS, CAROLYNN TALLEY and R. V. PLATOU, Pediatrics **5**:241 (Feb.) 1950.

The authors demonstrate that characteristic dermatoglyphic features rank high in frequency among the variable stigmas which go to make up the syndrome of mongolism. It is believed that though they are not diagnostic alone, these objective, measurable and unchanging evidences of mongolism seen in hand prints should be helpful in establishing an early diagnosis. Dermatoglyphic features indicative of mongolism ranked high in frequency among stigmas reported for typical examples of mongolism by 82 physicians. The technic for preparing prints is a simple one which requires very little practice for perfection; interpretation based on the empiric but definite criteria defined by the authors can be accomplished with relative ease. These findings are in keeping with the suggestion that factors responsible for the occurrence of mongolism are operative prior to the third month of fetal life and are consistent with known facts concerning embryologic development of epidermal ridges of the palms.

FROM THE AUTHORS' SUMMARY.

THE ROLE OF A PSYCHIATRIC CLINIC FOR CHILDREN. RAYMOND T. BINNS, Clin. Rep. Adelaide Children's Hosp. **1**:147 (Nov.) 1948.

The need for psychiatric clinics for children is shown by a study of patients seen in such a clinic over a period of 12 months. Fifty per cent of these children required active psychotherapy. Intensive study of the causes of behavior disorders can best be carried out in such a clinic.

McGUIGAN, Evanston, Ill.

NEUROLOGICAL STUDY OF TWO CASES OF CONSTITUTIONAL AND FAMILIAL PRECOCIOUS PUBERTY. M. SCHACHTER, Ann. pædiat. **172**:173 (March) 1949.

The clinical description of two boys with constitutional and familial pubertas precox who were at the same time analyzed by means of the Rorschach test is given. The somatic and psychological peculiarities of these two cases are mentioned; they are apparently identical, judging from the results of the individual investigation. This individualization gives pointers for the medical and pedologic treatment.

FROM THE AUTHOR'S SUMMARY.

PSYCHOPHYSIC CORRELATIONS: SCHIZOPHRENIA AND LIVER METABOLISM. F. GEORGI, R. FISCHER, R. WEBER and P. WEIS, Schweiz. med. Wchnschr. **78**:1194 (Dec. 11) 1948.

The hippuric acid test is used in its usual form. After an intervening day sodium benzoate and aminoacetic acid are given together. In this manner it can be determined whether a diminished excretion of hippuric acid is due to a lack of disposable aminoacetic acid. In acute stages of schizophrenia such liver dysfunctions can occur.

AMBERG, Rochester, Minn.

SCHIZOPHRENIA IN CHILDHOOD. PETER MOHR, Schweiz. med. Wchnschr. **79**:856 (Sept. 17) 1949.

It is pointed out that schizophrenia occurs rather rarely in the first decade of life. The case of a 9 year old boy is reported. From early childhood, his relations with his environment and other children was deficient. He had ideas of being poisoned and experienced a real notion of world destruction, which is often observed in adults as an initial symptom of schizophrenia but which seems to be very rare in children.

AMBERG, Rochester, Minn

NARCOSIS AND SLEEP. G. MANSFIELD, Wien. klin. Wchnschr. **60**:796 (Dec. 10) 1948.

Narcosis produces complete suppression of cerebral activity—pain perception, voluntary motions and reflexes—whereas the intensity of cell metabolism is not altered. Sleep results from the activity of inhibition centers and is a state of decreased cell activity and diminished oxidations. For a detailed discusson, the paper must be consulted.

AMBERG, Rochester, Minn.

MATERNAL ILLITERACY AND ITS EFFECT ON THE BRINGING UP OF THE CHILD. V. L. BALDASSERINI, Lattante **19**:465 (Aug.) 1948.

As many as 20 per cent of the mothers who brought their children to the Pediatric Clinic in Perugia were illiterate, and only 16 per cent had had schooling beyond the fifth grade. However, in a local textile mill less than 2 per cent were found illiterate and over 55 per cent had had schooling beyond the fifth grade. Examples are cited of cases in which the illiteracy of the mother had caused injury to the baby's health, such as errors in feeding, especially when breast feeding was no longer possible. Also there have been cases in which extensive tuberculous lesions have developed in the child and cases of poisoning from improper medication. Better school facilities, especially in the country areas, establishment of infant asylums and of adult educational centers and a civic awakening are advised to remedy this high incidence of illiteracy.

HIGGINS, Boston.

AN INFANTILE MANNER IN SPREADING THE FINGERS. P. ROBOZ, Paediat. danub. **4**:215 (Oct.) 1948.

A certain characteristic position may be observed in children if they spread their fingers with an extended and prone arm. In adults the forearm and the back of the hand either remain

at the same height or the hand is somewhat lowered but the fingers are always held at the same level. In many children the back of the hand and the fingers take a vertical position when the fingers are spread. The fingers are held at different levels, as though they want to grasp something. This infantile manner of spreading the hand is quite common in young children but disappears with age. It was found characteristic of mentally backward children even in older age groups. The phenomenon is considered to be of extrapyramidal origin.

FROM THE AUTHOR'S SUMMARY.

Diseases of Muscles, Bones, Joints and Lymph Nodes

EPIPHYSEAL DESTRUCTION BY FROSTBITE. H. E. THELANDER, J. Pediat. **36**:105 (Jan.) 1950.

Thelander reports the case of a boy 9 years of age with absence of the epiphyses of the distal and middle articulations of the second to fifth digits of the right hand. He had sustained an extremely severe frostbite of this hand 2½ years previously.

MACDONALD, Pittsburgh.

PATHOLOGICAL QUESTIONS RELATED TO MUSCULAR DISEASE: MYOGLOBIN METABOLISM. GINO MELDOLESI, Bull. d. schweiz. Akad. d. med. Wissensch. **6**:35 (March) 1950.

The author discusses the metabolism of myoglobin in healthy and in myodystrophic human beings and reviews the results of the researches hitherto published on this subject. He shows that myoglobin has a metabolism of its own and is independent of the coloring matters of the blood. The formation of myoglobin takes place in the fibers of the muscles, where it is formed through the union of a monomolecular heme with a globin of low molecular weight. Bilifuscin as a product of degradation is discussed. Its chemical structure causes it to be a dipyrrole. Other dipyrroles are discussed, and the author examines their possible identity or affinity with bilifuscin. The adaptation of these results to the clinic for myopathic patients gives the following results:

1. In each patient with myopathia the nature of the synthesis and degradation of the myoglobin can be followed, and it is possible to decide whether one has to deal with a primary or secondary myopathia.

2. In cases of primary myopathia one can ascertain whether the systematic discoloring of the striated muscles is due to an exaggerated degradation or to an insufficient synthesis of the myoglobin or whether it must be considered as the result of a disequilibrized metabolism of the myoglobin. The author also examines the importance of vitamin E for the metabolism of myoglobin.

FROM THE AUTHOR'S SUMMARY.

THE ROLE OF HORMONES IN GROWTH AND AGING OF THE SKELETON AND THEIR SIGNIFICANCE FOR THE PATHOGENESIS OF ARTHRITIS DEFORMANS. M. SILBERBERG and R. SILBERBERG, Schweiz. med. **79**:127 (Feb. 12) 1949.

This paper gives a good review of the role various hormones play in the growth of the skeleton.

AMBERG, Rochester, Minn.

ARTHROGRYPOSIS MULTIPLEX CONGENITA: A DISEASE OCCURRING NOT TOO RARELY BUT NOT TOO OFTEN DESCRIBED. MANUEL BASTOS-ANSART, Schweiz. med. Wchnschr. **80**:564 (June 3) 1950.

The disease is characterized by the presence of contractures on all four extremities. Sometimes the arms are more affected than the legs or vice versa. Hands and feet are in adduction, elbows and knees in extension. Shoulders and hips need not be deformed but participate in the striking rigidity of the extremities. The joints themselves are not injured, and roentgenograms show normal development. In most cases multiple arthrogenic contractures exist, which account for the name, arthrogryposis multiplex congenita.

The disease occurs more frequently than has been supposed. It has not been described more frequently because of various circumstances. Infants having it are often nonviable, or the disease is transitory so that it can be observed only for a few days or months. Sometimes one of

the deformities, such as a clubfoot, is so striking that the affliction of the rest of the extremities is overlooked.

The author was able to collect 30 cases from histories of cases seen in the course of years. It occurs preferentially in girls in a ratio of 4:1. There is no evidence of hereditary factors. The muscles which were examined were transformed nearly entirely into fibrous tissue. Other parts of the soft tissues are usually also affected. The orthopedic treatment is discussed.

AMBERG, Rochester, Minn.

RETICULOSARCOMA OF THE LYMPH NODES (MIKULICZ SYNDROME). E. MENOZZI, Lattante **19**:471 (Aug.) 1948.

Menozzi reports the case of a girl of 3 years who presented the picture of reticulosarcoma of the lymph nodes (Mikulicz syndrome). The glandular swellings were accompanied with anemia. Biopsy of a lymph node and a bone marrow smear established the diagnosis of reticulosarcoma.

HIGGINS, Boston.

MALIGNANT LYMPHOGRANULOMA IN A CHILD. LAURA MELE, Lattante **20**:12 (March) 1949.

In a boy of 3 years a supraclavicular swelling due to matted lymph nodes developed. A biopsy revealed loss of normal lymph node tissue and the presence of epithelioid cells, plasma cells and scar tissue. A diagnosis of malignant lymphogranuloma was made, and six x-ray treatments of 200 r were given over the mass. Six months later this glandular mass had essentially disappeared and no other enlarged lymph nodes were present. The spleen, however, had gradually increased in size. At this time the child had no fever, no anemia or other clinical symptoms or signs of the disease.

HIGGINS, Boston.

MULTIPLE CARTILAGINOUS EXOSTOSES (HEREDITARY DEFORMING CHONDRODYSPLASIA). FUN-YONG KHOO, PING-YI CHANG, CHING-TAN LEE and KUO-SHENG FAN, Chinese M. J. **66**:252 (May) 1948.

Multiple cartilaginous exostoses are not uncommon. When the deformities are mild, they may escape detection unless searched for. When confronted with a single exostosis or abnormal diaphysial development, one should obtain roentgenograms of the entire skeleton. A solitary exostosis is usually not important; a number of exostoses in a single patient may be serious and may be associated with abnormal development of bones.

Seven cases of multiple cartilaginous exostoses in Chinese are reported. In all cases but one a definite hereditary trait was shown.

MACDONALD, Pittsburgh.

INFANTILE CORTICAL HYPEROSTOSES: REPORT OF A CASE. KATHERINE T. CHEN and TING-SING YU, Chinese M. J. **66**:266 (May) 1948.

The authors report a case of infantile cortical hyperostoses in a male infant who was seen first at the age of 6 weeks. At that time only the long bones were affected. At the age of 6 months the mandible became involved. At the age of 18 months the child was apparently well.

MACDONALD, Pittsburgh.

Diseases of the Eye

SURGERY OF CONGENITAL CATARACTS. F. C. CORDES, Am. J. Ophth. **31**:1073 (Sept.) 1948.

Cordes feels that vision of 20/40 or better should contraindicate surgical intervention in cases of congenital cataracts. If the opacities are sufficiently dense to hinder development of fixation, the first eye should be operated on at the age of 6 months and the second eye between the second and the fourth year. He favors Barkan's method of linear extraction.

W. S. REESE [ARCH. OPHTH.].

RETROLENTAL FIBROPLASIA IN PREMATURE INFANTS. W. C. OWENS and E. U. OWENS, Am. J. Ophth. **32**:1 (Jan.) 1949.

The authors found no retrolental fibroplasia at birth in 218 infants whose weight at birth was less than 4½ pounds (2,040 Gm.). Of these children, 111 were followed for six months

or more, and retrolental fibroplasia developed in five of this group. The development of retrolental fibroplasia was followed in nine premature infants. All visible remains of the hyaloid membrane had disappeared before the onset of the disease. The initially normal fundus was replaced by angiomatous dilatation of the retinal vessels, followed by massive retinal exudation, retinal detachment and the formation of a retrolental membrane by fusion of the peripheral folds of detached retina.

W. S. Reese [Arch. Ophth.].

Congenital Cataracts. C. H. Bagley, Am. J. Ophth. **32**:411 (March) 1949.

This article is a statistical survey of 87 cases. Bagley concludes that better results are obtained when operation is done after the age of 4 years and that needling does not give as good results as linear extraction, or as needling followed by linear extraction.

W. S. Reese [Arch. Ophth.].

Retrolental Fibroplasia in Prematurely Born Children. A. P. Gilger, Am. J. Ophth. **32**:917 (July) 1949.

Gilger made a survey of retrolental fibroplasia in a series of 229 prematurely born children weighing less than 2,268 Gm. at birth, observed during a five year period. No cases of retrolental fibroplasia were found in the group weighing above 1,814 Gm. at birth. Of 96 infants with birth weights of 1,814 Gm. or less, seven, or 7.3 per cent, were found to have retrolental fibroplasia.

In this study the predominance of boys over girls among the infants affected with retrolental fibroplasia was statistically significant.

The following factors were considered in the etiology of retrolental fibroplasia: uterine bleeding during pregnancy, age and parity of the mother at delivery, occurrence of virus infections or chronic illness during pregnancy, cause of premature onset of labor, race, associated intracranial disease, administration of vitamin A in early postnatal life, and other factors in early postnatal management and course. The difference in the influence of these factors in affected and in nonaffected premature infants was not sufficient to be statistically significant, and therefore the development of retrolental fibroplasia in this series cannot be attributed to them.

Three cases in which the infants were followed from birth until the development of retrolental fibroplasia are described.

W. S. Reese [Arch. Ophth.].

Factors in the Diagnosis of Squint. Vernon L. Lindberg, Minnesota Med. **32**:492 (May) 1949.

The author discusses one type of squint, namely, the monocular convergent. This is one of the commonest muscle problems found in infancy and childhood. A condition known as "epicanthal folds" has been shown as a source of error in determining the presence of squint. The "corneal reflex test" and the "cover test" have been described and suggested as aids in detecting cases of false squint. Two important reasons for early diagnosis and treatment of this condition before school age have been indicated.

Stoesser, Minneapolis.

Nevoxantho-Endothelioma with Ocular Involvement. Harvey Blank, Paul G. Eglick and Herman Beerman, Pediatrics **4**:349 (Sept.) 1949.

Nevoxanthoendothelioma is a benign nevus with xanthomatous changes. It appears at birth or shortly thereafter. The process may occasionally be mistaken for sarcoma but usually follows a benign course with crops of new lesions which eventually tend toward spontaneous involution. The case reported demonstrates that the eye can be involved with lesions having the same histological structure as those of the skin. Because of the favorable course of patients suffering from this disease and the realization that visceral lesions may occur in nevoxanthoendothelioma, early diagnosis insures an accurate favorable prognosis.

From the Authors' Summary.

USE OF ANTI-ALLERGIC DRUGS IN THE TREATMENT OF PHLYCTENULAR OPHTHALMIA. C. F. BOWES, Brit. J. Ophth. **32**:163 (March) 1948.

In 15 typical and active cases of phlyctenular ophthalmia the photophobia, lacrimation, irritation and eczema showed no improvement with diphenhydramine (benadryl®) hydrochloride and antazoline (antistine®) hydrochloride, two well recognized antiallergic drugs. All the patients showed positive reactions in the Mantoux test and roentgen ray evidence of tuberculous infection.

W. ZENTMAYER [ARCH. OPHTH.].

PIGMENTARY DEPOSITS IN THE RETINA. F. SILVAN LÓPEZ, Arch. Soc. oftal. hispano-am. **8**:443 (March) 1948.

Two cases of pigmentary deposits in the retina previously misinterpreted as nevus formations in the choroid are reported. In a girl aged 15 no abnormality was found on routine examination of the eyes except a number of slate-colored plaques in the lower nasal quadrant of the retina of the left eye. The plaques were arranged in groups, the number ranging from a single one, near the papilla, to collections of 15 or 20, located more peripherally. The impression was obtained that the groups were originally single large plaques. The intensity of the pigment decreased with the distance of the plaque from the disk. The spots were discrete and were definitely located over the choroidal vessels, occluding them. Another patient, a girl aged 10, with strabismus of the left eye and congenital amblyopia, had pigmentary deposits in the retina. A total of 12 well defined, dark slate-colored spots were seen located over the choroidal vessels on the nasal side of the retina approximately 8 disk diameters from the papilla.

H. F. CARRASQUILLO [ARCH. OPHTH.].

PERSISTENT PUPILLARY MEMBRANE. EUGENE CHAN, Chinese M. J. **66**:29 (Jan.) 1948.

The cause of persistence of the pupillary membrane is obscure. Persistence of the normal structures may possibly be the result of metabolic disturbances in the fetus at or after the fifth month. It has been suggested that persistence with abnormal involvement of the lens capsule may be the result of an inflammatory process. Chan reports a case of bilateral persistence of the pupillary membrane in a 20 year old youth.

MACDONALD, Pittsburgh.

CAUSES OF BLINDNESS IN CHINA. WILFRED STEPHEN FLOWERS. Chinese M. J. **66**:38 (Jan.) 1948.

It is impossible to obtain reliable statistics concerning the incidence and etiology of blindness in China. The author has studied reports from hospitals and outpatient departments in various parts of the country, and these are the basis for his report. The incidence of blindness is undoubtedly high.

The commonest causes of blindness in China, not necessarily in the order of their importance, are (1) trachoma; (2) ulcerative keratitis; (3) mucopurulent conjunctivitis; (4) phlyctenular conjunctivitis; (5) ophthalmia neonatorum; (6) smallpox, and (7) keratomalacia.

MACDONALD, Pittsburgh.

TRACHOMA IN CHANGSHA. CHEN-CHUNG WU, Chinese M. J. **66**:144 (March) 1948.

From September 1946 to March 1947 there were 1,340 patients seen in the eye clinic of Hsiang-Ya Hospital. Of these, 1,017 (75.88 per cent) suffered from trachoma. Of these, 7.7 per cent were under 10 years and 20.5 per cent were between 10 to 20 years.

MACDONALD, Pittsburgh.

Cutaneous Diseases; Allergy

FAMILIAL BENIGN CHRONIC PEMPHIGUS. R. B. COLES, Proc. Roy. Soc. Med. **43**:61 (Feb.) 1950.

Several case reports of familial benign chronic pemphigus were presented by several clinicians. There were reports concerning light sensitization of the skin, congenital ichthyosis, chronic granuloma of the nose and localized pili torti.

HEARD, Monterey, Calif.

HISTOPATHOLOGY AND ETIOLOGY OF ERYTHEMA NODOSUM. G. MIESCHER, Bull. d. schweiz. Akad. d. med. Wissensch. **6**:172 (March) 1950.

The histopathology of the lesions of erythema nodosum has been extensively examined by the author. The lesions regularly showed a specific granulomatous formation which could not be identified with any other known granuloma. This indicates that erythema nodosum is an infectious condition sui generis and that infections which are very often observed in connection with it, especially tuberculosis, have only the importance of provoking factors analogous to the relation of malaria and pneumonia to herpes simplex. FROM THE AUTHOR'S SUMMARY.

THE EFFECT OF LACTOFLAVIN (VITAMIN B_2) ON THE SKIN CAPILLARIES AND ON THE RATE OF ABSORPTION OF EDEMA. P. NICOLAJ, Clin. pediat. **31**:226 (April) 1949.

Vitamin B_2 (1 to 20 mg.) when given to children did not affect the capillary fragility, but it did lengthen the time of absorption of an induced edema. HIGGINS, Boston.

RECOGNITION AND TREATMENT OF MICROSPORIA. N. KRUSPE, Med. Klin. **20**:622 (May 19) 1950.

The author observed 10 boys and 2 girls, 4 to 10 years of age, who were infected with Microsporum audouini. In children this infection is localized in the scalp and penetrates into the hair follicles. It is rarely limited to a single focus; usually four to 10 foci can be delineated, the oldest of which may reach a diameter of 5 to 6 cm. The picture is similar to that of trichophytosis. The infection is readily transmitted but has the peculiarity of healing spontaneously during puberty. The epilation treatment is carried out with x-rays or with oral administration of thallium acetate in a dose of 8 mg. per kilogram. It is important that the treatment is carried out with all due precautions. Treatment is followed by application of disinfecting and antimycotic applications. Clothing, toilet utensils, bedding and rooms are to be disinfected. AMBERG, Rochester, Minn.

Surgery and Orthopedics

ANESTHESIA IN CHILDHOOD. MARY BURNELL, Clin. Rep. Adelaide Children's Hosp. **1**:134 (Nov.) 1948.

The various techniques of pediatric anesthesia are discussed. Careful attention to the patient is essential, and as light a plane of anesthesia as possible should be used.

McGUIGAN, Evanston, Ill.

NAILING AND LATE RESULTS OF FRACTURES OF THE NECK OF THE FEMUR AND OF SEPARATION OF THE EPIPHYSIS. GEORG SALEM, Wien. klin. Wchnschr. **61**:152 (March 11) 1949.

Fractures of the neck of the femur are relatively rare in youth. The results of treatment including nailing are given for five patients 10 to 17 years of age. In three cases the results were satisfactory; in two a necrosis of the head of the femur occurred, such as occurs not infrequently with conservative treatment. It is advised that operation be done two to five days after injury. No load should be permitted earlier than after six to eight weeks. X-ray examination should be done every four weeks, and the nail should be removed as soon as solid bony cure is obtained.

The late results of nailing are much better in patients with separation of the epiphysis, which occurs only at an age between 9 and 18 years, that is, during a period of rapid growth. For seven of eight patients full function and freedom from symptoms were noted. Most of these patients were observed for more than 10 years. In these cases injuries may play a secondary role. Most of the children are excessively large, fat and slack.

AMBERG, Rochester, Minn.

Teeth and Dentistry

FLUORINE AND DENTAL CARIES. H. TRENDLEY DEAN, Illinois M. J. **95**:33 (Jan.) 1949.

Too much fluorine in domestic water results in the deformity of the enamel known as endemic dental fluorosis; too little, a high dental caries incidence. The amount of fluorine required to inhibit markedly dental caries attack is sufficiently low to eliminate the complicating problem of endemic dental fluorosis found among users of higher fluoride waters. This phenomenon could be converted into a practical means for controlling dental caries *en masse* through the medium of the public water supply.

To test the fluorine-dental caries hypothesis, a study was made at Galesburg and Quincy, Ill. The Galesburg water supply contains 1.8 parts per million of fluoride; the Quincy water supply, obtained from the Mississippi River, is practically free of fluoride. The dental caries incidence in the 306 Quincy children studied was well over three times that observed in the 319 Galesburg children studied. It was apparently in this study that the factor responsible for the low amount of dental caries in the city was operative irrespective of whether the child showed macroscopic evidence of dental fluorosis or not.

An enlarged study of 21 cities providing a wide variety of dissimilar conditions was then undertaken. These cities present a wide diversity in types and sources of water supplies, not only in regard to fluoride concentration but also in regard to other mineral constituents. In this study a total of 7,257 white urban school children in the 21 cities were examined. All the children had been continuously exposed throughout life to the variable under investigation (the common water supply). Children using domestic waters containing as little as one part per million of fluoride experienced only about a third as much dental caries as children in comparable groups using a water that contained no fluoride. Other independent studies in the United States, England, South Africa, Argentina and India report similar findings regarding the influence of small amounts of fluorides on the amount of dental caries in the community. Bacteriologic, chemical and animal experimentation consistently support the epidemiological findings.

A fluorine prophylaxis has been demonstrated by means of a topical application. A minimum of four treatments which may be given a week apart is essential.

BARBOUR, Peoria, Ill.

TOOTHBUD INFECTION OF INFANTS. O. LADE, Kinderärztl. Praxis **16**:146 (May-June) 1948.

Abscess of the right side of the upper jaw was noted on a less than 1 month old child. It led to sequestration of part of the right maxilla. At the time of occurrence there was no evidence of other infection; in the course of the illness, however, infections of the breast, the middle ear and the eyelid occurred. The child had disturbances of tooth development consisting of the presence of a lower incisor at 14 days of age. The child recovered from the infection without the use of chemotherapy but with defects of his denture.

GLASER, Chicago.

Miscellaneous

LEAD POISONING DIAGNOSED BY THE PRESENCE OF NUCLEAR ACID-FAST INCLUSION BODIES IN KIDNEY AND LIVER. M. WACHSTEIN, Arch. Path. **48**:442 (Nov.) 1949.

The finding of nuclear acid-fast inclusion bodies in liver and kidney tubule cells gave the clue to the cause of death of a 21 month old white boy. The child had been admitted to the hospital for increasing irritability of four weeks' duration and recent vomiting. He was found on examination to be dehydrated, drowsy and pale. Positive findings included signs of central nervous system and cardiac disorder. Laboratory findings revealed anemia. Despite supportive therapy, he lapsed into coma and died. At autopsy there were found minimal gliosis and loss of Purkinje cells of the brain, focal subacute myocarditis, fatty changes of the liver and chronic bronchitis. On observing the presence of intranuclear inclusion bodies in the liver and kidney tubule cells, the possibility of lead poisoning was suspected. Chemical examination of the kidney and liver was made and revealed a lead content far above normal. Requestioning of the parents divulged the information that the child had the habit of putting objects in his mouth frequently. The author considers the presence of acid-fast intranuclear inclusion

bodies typical of lead poisoning. The property of acid fastness belongs only to the inclusion bodies caused by lead and bismuth. Although the clinical signs and symptoms were predominantly those of central nervous system disturbance, microscopic examination of the brain did not reveal typical signs of lead encephalitis. The changes present were compatible with but not characteristic of lead encephalitis. The myocardial findings were also nonspecific.

CHAN, San Francisco.

...LURONIDASE. JOSEPH SCHWARTZMAN and MORRISON LEVBARG, J. Pediat. **36**:79 (Jan.) 1950.

...yaluronidase, the spreading factor, promises to be a useful new drug. It facilitates the ...utaneous absorption of a variety of fluids, including calcium gluconate, penicillin and ...omycin. The optimum dose is apparently 500 viscosity units. No toxic reactions have ...cu... and drug sensitivity is uncommon. Schwartzman and Levbarg have used the drug ... a ...ty of situations, usually with success. They have found that salicylates inhibit the ...ction ...yaluronidase. They also found that subcutaneous absorption was delayed when the patient's total serum protein level fell below 5.5 per cent.

MACDONALD, Pittsburgh.

DEATH OF CESAREAN INFANTS: A THEORY AS TO ITS CAUSE AND A METHOD OF PREVENTION. DANIEL B. LANDAU and HOWARD B. GOODRICH, J. Pediat. **36**:421 (April) 1950.

Some infants delivered by cesarean section present peculiar difficulties in initiating respiration. Some others are apparently well until a few hours after birth; then severe signs of respiratory distress develop and the infants die within a matter of hours. The authors believe that these infants suffer from hematogenic shock, the cause of which is the immediate clamping and cutting of the umbilical cord, which deprives the infant of a considerable amount of blood which he would ordinarily receive under conditions of a normal delivery. To correct this, the authors remove the placenta from the uterus with the infant. The cord is not clamped or cut. The placenta is wrapped in a towel and suspended from a standard. After six to 10 minutes when the cord vessels have collapsed, the cord is cut and tied in the usual manner. In a series of 87 infants delivered by cesarean section and treated in this manner no cases of "delayed shock" were seen.

MACDONALD, Pittsburgh.

SULFONAMIDE DOSAGE IN EARLY INFANCY. J. B. RICHMOND, H. KRAVITZ and W. SEGAR, J. Pediat. **36**:539 (May) 1950.

Sulfonamides are excreted through the kidneys in a manner similar to urea. Urea clearances are abnormally low in premature, newborn and young infants. Sulfonamides are not excreted rapidly in these infants, and, as a result, satisfactory therapeutic blood levels can be maintained with infrequent doses. The authors prefer the subcutaneous to the oral method of administration because it is more efficient.

MACDONALD, Pittsburgh.

PRESENT TRENDS IN PENICILLIN THERAPY. SAM BOYER JR., Minnesota Med. **31**:1305 (Dec.) 1948.

This is an up-to-date discussion on penicillin therapy, and emphasis is placed on the fact that penicillin is used promiscuously, widely and frequently without indication. Bacteriologic study and diagnosis are lacking more frequently than they are found. Reactions to penicillin, usually allergic, may occur. The development of penicillin procaine during recent months has been a far reaching step in prolonging the activity of the drug. The inhibition of renal excretion may be of value in the prolongation of penicillin activity.

STOESSER, Minneapolis.

STUDIES OF PENICILLIN IN PEDIATRICS: III. PROCAINE PENICILLIN G IN SESAME OIL, IN PEANUT OIL WITH 2% ALUMINUM MONOSTEARATE AND IN WATER WITH SODIUM CARBOXYMETHYLCELLULOSE. B. M. KAGAN, M. NIERENBERG, D. GOLDBERG and A. MILZER, Pediatrics **5**:664 (April) 1950.

This report gives pertinent data on the serum penicillin concentrations 12 and 24 hours after intramuscular injection of penicillin G potassium in peanut oil and in beeswax, which is fluid

at room temperature, and of three different penicillin procaine preparations. These three preparations are penicillin G procaine in sesame oil, penicillin G procaine in peanut oil with 2 per cent aluminum monostearate and penicillin G procaine in water with sodium carboxymethylcellulose. When administration was in a dose of 8,000 units a pound (0.5 Kg.) to infants and children weighing between 4.5 and 18.0 Kg., there was no statistically significant difference in the serum levels obtained. A dosage schedule for these preparations is suggested for pediatric use. The aqueous preparation offers some advantages, which are discussed. Experiences are reported which emphasize the necessity of avoiding intravenous administration of all these preparations.

FROM THE AUTHORS' SUMMARY.

CLINICAL STUDIES OF THE EFFECTS OF 3,5,5-TRIMETHYLOXAZOLIDINE-2-4-DIONE (TRIDIONE®) ON THE HEMATOPOIETIC SYSTEM, LIVER AND KIDNEY. ERIC DENHOFF and MAURICE W. LAUFER, Pediatrics **5**:695 (April) 1950.

Six children receiving trimethadione (triodione®) in clinical dosage were studied over periods ranging from six to 16 months, with tests being made of both peripheral blood and bone marrow. There was a constant syndrome of a decline in bone marrow megakaryocytes and nucleated red blood cell elements, a low peripheral blood thrombocyte (platelet) count and prolonged clot retraction time. There was an occasional association of peripheral leukopenia, toxic signs in the red blood cells and lymphocytes and an abnormal cephalin flocculation response. Withdrawal of the medication caused a return to normal values, most rapid and marked in the bone marrow.

It is possible that an aplastic response might have occurred in some of these patients if administration of the drug had been continued in high dosage. Since peripheral leukopenia was only an occasional finding, dependence on this test alone might fail to indicate that such a process was going on. In this study the simplest and most reliable technic to use as a single indicator seemed to be the clot retraction time. The danger point was felt to be a delay in clot retraction to initial retraction, two hours or more; definite retraction, three hours or more. Bone marrow studies, though less readily available, were quite valuable also. A depression of megakaryocytes could be of particular significance in suggesting possible trimethadione sensitivity early. If the megakaryocyte level spontaneously returned to normal, even while the patient continued to receive medication, it was probably safe to continue with the trimethadione. A persistence of a low megakaryocyte value was, however, regarded as a danger signal.

FROM THE AUTHORS' SUMMARY.

CLINICAL RECOVERY FOLLOWING PROLONGED ANURIA IN AN INFANT TWO MONTHS OF AGE: REPORT OF A CASE OF POTASSIUM BROMATE INTOXICATION. S. A. WARREN and W. V. GROSS JR., Pediatrics **5**:954 (June) 1950.

A case of prolonged (107 hours) renal shutdown due to potassium bromate poisoning is presented. Emphasis is placed on the extreme youth of the patient and on his clinical recovery on a conservative regimen. There is included a brief description of the management, which consisted in fluid and electrolyte restriction. A review of the pertinent literature is given.

FROM THE AUTHORS' SUMMARY.

CENTRAL INHIBITORY EFFECTS OF CARBON DIOXIDE: II. MACACUS RHESUS. S. N. STEIN and G. H. POLLOCK, Proc. Soc. Exper. Biol. & Med. **70**:290 (Feb.) 1949.

The previous work of one of the authors revealed that carbon dioxide prevents electrically induced cortical seizures in cats. Inasmuch as the normal electroencephalograph of the Macacus rhesus is well known and it is possible to extrapolate from it to the human electroencephalograph, this animal was chosen for further study. Monkeys were fitted with bilateral screw in electrodes and immobilized with dihydro-beta-erythroidine and received artificial ventilation with various concentrations of carbon dioxide in oxygen. Concentrations of carbon dioxide over 20 per cent, when inhaled for three minutes, prevented the electrically induced seizures.

HANSEN, Galveston, Texas.

CARONAMIDE: ITS DOSAGE AND USE AS AN ENHANCING AGENT IN PENICILLIN THERAPY IN CHILDREN. GAVIN HILDICK-SMITH, South African M. J. **24**:24 (Jan. 14) 1950.

The author discusses the use and mode of action of carinamide in increasing penicillin blood levels. He notes that its action is not constant but that it may be very useful against infections with penicillin-resistant organisms. Two illustrative cases are presented.

McGUIGAN, Evanston, Ill.

THE EFFECT OF CARONAMIDE UPON THE PENICILLIN-CONCENTRATION OF THE BLOOD. M. R. H. STOPPELMAN, Ann. pædiat. **174**:375 (June) 1950.

The effect of carinamide on the penicillin level in the serum of infants and older children has been investigated. A rise of the penicillin concentration and maintenance of penicillin in the blood during a longer period were obtained in most cases by the daily administration of 0.4 Gm. of carinamide per kilogram of body weight. This effect was observed in those cases in which penicillin in saline solution was used as well as in the cases in which one injection of 300,000 units of penicillin in oil was given. The administration of carinamide, apart from nausea and vomiting, caused no toxic symptoms. In special cases carinamide may prove to be valuable in reducing the number of penicillin injections and in obtaining high penicillin levels in the blood.

FROM THE AUTHOR'S SUMMARY.

HYPERSENSITIVITY REACTIONS TO MERCURY MEDICATION IN CHILDREN WITH SPECIAL REFERENCE TO CALOMEL DISEASE. G. FANCONI, A. BOSTSZTEJN and P. SCHENKER, Helvet. paediat. acta, 1947, vol. 2, supp. 4, no. 2.

A report is given of 59 cases of anaphylactic reactions to mercury after the application of mercury ointment and the internal administration of mild mercurous chloride (calomel).

The local application of mercury may cause a local or general exanthem and dermatitis with or without a general febrile reaction.

Special attention may be drawn to the disease following mild mercurous chloride (39 cases), which generally occurred about the eighth day after administration. The drug was given usually in cases of intestinal parasitism. The chief symptoms were fever; pronounced polymorphic exanthem (the maculae being scarlatiniform in the first days but later becoming larger and irregular); leukopenia with eosinophilia; general glandular swelling, and sometimes hypertrophy of the spleen. The course is generally benign. More serious complications, like general and persistent dermatitis, spontaneous relapse, meningoencephalitis and agranulocytosis, can take place. The administration of mild mercurous chloride should thus be avoided in the treatment of intestinal parasitism.

Mild mercurous chloride produces a change in the defense mechanism of the organism. An attack confers immunity in the majority of children, that is, further administration of the drug does not cause a recurrence of the disease. If mercury treatment is previously given, an accelerated reaction, such as serum disease, may appear after administration of mild mercurous chloride. During the climax of this disease the dopa reaction (Block's reaction) was positive, but in the later stages only a few patients had positive reactions. The great clinical resemblance of the disease due to mild mercurous chloride and that due to barbiturates is striking. They are allergic conditions.

A report is also given of cases of polyradiculoencephalitis and Feer's disease (erythredema polyneuropathy) which occurred as late neuroallergic reactions due to mercury.

In two cases of mercury lipid nephrosis it was difficult to decide whether an allergic or a toxic reaction preponderated.

FROM THE AUTHORS' SUMMARY.

BLOOD CONCENTRATION OF SULFATHIAZOL ADMINISTERED TO HEALTHY SUBJECTS BY AEROSOL. G. CALZETTI and M. LATO, Clin. pediat. **30**:413 (July) 1948.

Observations were made of the blood concentration of sulfathiazole in healthy subjects, five adults and 37 children (3 months to 13 years of age), after a 20 per cent solution of a sulfathiazole preparation was inhaled. The absorption was very rapid, the drug content in the blood 15

minutes later being as high as when intravenous injection of the drug had been used. The aerosol method of administering the drug would appear to be more rapid and more satisfactory, even in extrapulmonary disease, than the oral administration.

HIGGINS, Boston.

THE ACTION OF CHOLINE HYDROCHLORIDE ON THE ENERGY METABOLISM OF CHILDREN. A. DEGLI ESPOSTI, Clin. pediat. **31**:205 (April) 1949.

Administration of 0.50 Gm. of choline hydrochloride by mouth lowered the basal metabolism and the degree of the specific dynamic action from ingested protein in children 7 to 12 years of age. The drug acts as a depressant of the sympathetic nervous system and should be of benefit in cases of hyperthyroidism.

HIGGINS, Boston.

APPEARANCE OF THE CHILD IN SPANISH ART. L. L. ECHETO, Lattante **21**:172, (March) 1950.

An article on old and modern paintings and sculpture depicting children by Spanish artists is accompanied with several illustrations. Most of the older works have a religious setting.

HIGGINS, Boston.

SOME FACTORS WHICH CAN REDUCE THE ACTIVITY OF PARAAMINOSALICYLIC ACID (PAS) IN THE BODY. I. PISU and G. F. CODURI, Minerva pediat. **2**:32 (Jan.) 1950.

In vitro tests reveal that pancreatic and gastric juices react chemically on the hydroxyl radical and not on the amino radical of paraaminosalicylic acid. It is possible that other body enzymes may chemically reduce to some extent the bacteriostatic action of the drug. It would appear also that the hydroxyl radical of the paraaminosalicylic acid molecule is the important index of the drug's bacteriostatic action, inasmuch as Escherichia B. coli in broth reacts only on the hydroxyl radical of it.

HIGGINS, Boston.

THE FIRST CASE OF FAVISM OBSERVED IN LIGURIA IN A CHILD OF SARDINIAN PARENTAGE. G. SANSONE, Minerva Pediat. **1**:210 (May) 1949.

In a boy of 22 months a typical case of favism developed. The boy was of Sardinian parentage. It was the first case of the disease to have occurred in the city of Genoa or in the province of Liguria. Of the 23 patients whose cases were reported in the Italian medical literature during the past 25 years, many have been in families who had come from Sardinia. It has been suggested that the Sardinian favus bean, as distinguished from the Sicilian or Calabrian favus bean, may be the etiological agent. It is quite possible that the allergy to the bean developed while the child was in utero.

HIGGINS, Boston.

A CASE OF CORROSIVE SUBLIMATE POISONING CURED BY BAL. S. PETROCINI, Policlin. inf. **16**:655 (Dec.) 1948.

Administration of dimercaprol injection (BAL in oil) was begun very shortly after a 5 year old boy had swallowed a mercury bichloride tablet; vomiting had been induced shortly after he took the tablet. Urinary albumin and abnormal sediments had disappeared by the ninth day.

HIGGINS, Boston.

CLIMATOLOGY IN THE TREATMENT OF CHILDREN. J. GARCIA AYUSO, Acta pediat. españ. **86**:90 (Feb.) 1950.

In a very detailed manner Dr. Ayuso discusses the effect of various climatic factors, including air, water, altitude, minerals of water and soil and amount of sunlight.

He discusses the use of various climates in the treatment of diseases, mentioning the great variety of climates available within Spain for the treatment of various illnesses. He feels that pediatricians have not taken sufficient cognizance of these localities and that preventoriums and sanatoriums for children would be a very excellent thing in the building of a more robust youth.

ALLEN, Santa Fe, N. Mex.

AGE, FATAL DOSAGE AND THE AMOUNT OF ALCOHOL IN THE BLOOD IN CASES OF FATAL ETHYL ALCOHOL INTOXICATION. K. LINCK, Med. Klin. **45**:570 (May 5) 1950.

The fatal dose of ethyl alcohol is given as 2 to 3.5 Gm. per kilogram for adults. The fatal dose for children seems to fall about within these limits; hence, a special sensitivity of children, as has been claimed, cannot be substantiated.

AMBERG, Rochester, Minn.

INTRATHECAL ADMINISTRATION OF PENICILLIN. CHIEH SUNG, Chinese M. J. **66**:689 (Dec.) 1948.

Chieh Sung reports two cases in which convulsive seizures occurred after the intrathecal administration of penicillin. An infant 16 months of age had a fatal convulsion after the intrathecal administration of a 1 cc. solution containing 10,000 units of penicillin. He did not have meningitis. A 9 month old girl with meningitis had a convulsion immediately after receiving 40,000 units of penicillin in 2 cc. of isotonic sodium chloride intrathecally. Her convulsions lasted three hours. She died one week later.

MACDONALD, Pittsburgh.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

Alvah L. Newcomb, M.D., *President*

Regular Meeting, Oct. 24, 1950

Symposium on Rheumatic Fever

Pathologic Considerations. Dr. Stanley Gibson.

Prevention and Prophylaxis. Dr. Philip Rosenblum.

Any program that deals with the prevention of rheumatic fever requires the cooperation of many agencies. A long range plan extending through puberty is necessary. Physicians and teachers should be educated, and, later, the services of health, school and welfare agencies in the community should be coordinated. Physicians especially should be "rheumatic fever conscious." A rheumatic fever registry would be desirable.

The proper treatment and, so far as possible, the prevention of all Streptococcus infections should be stressed. Since rheumatic fever seems to be more prevalent in the underprivileged groups, proper living conditions, with prevention of dampness and overcrowding, are necessary.

A diet high in proteins and vitamins, especially vitamin C, and perhaps high in cholesterol, is desirable. Contact with persons who have acute infection should be avoided.

The administration of one of the sulfonamides or antibiotics before and after nose and throat operations and the extraction of teeth is recommended.

Early and complete treatment of rheumatic fever until the disease is definitely inactive and the use of antibiotics through puberty to prevent recurrence are desirable.

An active research program is essential in any endeavor that deals with prevention of rheumatic fever.

Community Service. Dr. Hugh McCulloch.

Rheumatic fever and rheumatic heart disease are a community problem. In the family group the patient is the focal point from which radiate various influences which are of considerable importance to the doctor in dealing with management of the patient. The family doctor is the most important person in the patient's environment and carries the principal load. He must supply adequate and correct information to the family and must see that some member of the family has the intelligence to see that the patient receives adequate care.

In the community aspect also the family doctor plays the leading role; back of him are the other medical professional services and resources, consultants and specialists. Then there is the group of persons who, in proper sequence, exercise supervision—nurses, public health workers, nutrition workers, teachers, occupational therapeutists and medical social workers. Hospitals and clinics for treatment, schools and camps closely allied, parks and playgrounds, all have a part in the situation. Housing enters greatly into the problem of rheumatic fever control. Education of all the groups concerned and transmission of information from one source to the point where it can be applied in the family require the cooperation of many agencies. There are various types of home services now being developed throughout the country, one of which, at La Rabida Jackson Park Sanitarium, is working well in its early stages. In this program stress is laid on the importance of the family physician as the key person, and effort is made to see that the family relationship is not disturbed by introduction of outside factors.

The umbrella of preventive medicine is really an application of medical science and medical knowledge to the various channels and various points in the control of rheumatic fever and rheumatic heart disease. The trend is in a favorable direction so far as morbidity and mortality are concerned. The potential number of rheumatic units in a community is probably large, but the number of individuals who have demonstrable lesions of rheumatic fever and rheumatic

heart disease is small in proportion to the potential number. Community services, therefore, must not be only directed toward the small group who are identified as having rheumatic fever and rheumatic heart disease, but instead the umbrella should spread over everyone who is a potential rheumatic patient.

Current Methods of Treatment. Dr. H. William Elghammer.

Treatment of rheumatic fever during the past 25 years has been empiric, based on predisposing causes and symptoms of the disease. This basic treatment has from time to time been supplemented with a variety of specific therapeutic measures, such as removal of tonsils, attempts to produce immunity by convalescent serums and vaccines, desensitization by injection of streptococcic products and the use of chemotherapy and antibiotics. None have proved to be of therapeutic value, and some have been observed to increase the severity of the rheumatic process.

The marked familial tendency, the high incidence of onset before puberty and the failure of various specific measures lead one to doubt that rheumatic fever is an infectious process and suggest that it is metabolic in nature, that the collagenous tissue responds to environmental changes and produces the picture we recognize as rheumatic fever, with the possibility that some exogenous agent may act as the trigger mechanism.

Pain and fever are alleviated by administration of salicylates, although many observers feel that they exert only an analgesic and antipyretic action. However, it is a common observation that tachycardia and sedimentation rate are often reduced by salicylate medication, and it would seem that these drugs may have a supportive action and possibly some effect on the pathologic process. Isolation of the patient is of major therapeutic value in the protection against infectious agents and in reduction of stress and strain.

The use of pituitary adrenocorticotropic hormone (ACTH) in treatment of rheumatic fever is still in the experimental stage. Some 20 cases have been studied at La Rabida Jackson Park Sanitarium. The early patients had recurrent active rheumatic fever with heart failure or impending heart failure; eight patients had recurrent active disease with less severe carditis. Four of the 20 patients died. The most striking effect noticed was that of euphoria, or general well-being, appearing usually within 12 to 24 hours after the initial dose. The patient became cooperative and alert, and there seemed to be an increase in muscle tone and turgor. A marked increase in appetite, resulting in rather startling weight gains when food intake was not limited, was also noted. Temperature and sedimentation rate returned to normal, and subcutaneous nodules and skin rashes disappeared.

The cardiac status improved in many cases; tachycardia and the size of the heart decreased; disappearance of middiastolic murmur and changes in character of the murmur were noted. Friction sounds diminished or disappeared. Electrocardiographic changes were rather irregular, but shortening of prolonged P-R intervals was seen in some cases. In general, changes from active carditis to the quiescent phase seen under empiric management with salicylates and digitalis have taken place with administration of ACTH in rather dramatic fashion and within a few days.

Salt and water retention with potassium depletion and alkalosis may occur; a persistent increase in blood pressure has been noted; a rounding of the face, with variable degrees of acne and, in two instances, evidence of hirsutism occurred. At variable intervals after withdrawal of ACTH, some patients showed recurrences and in others there was activity of moderate degree.

There is as yet no accurate laboratory method for determination of dosage or estimation of response to the drug. It is thought that the drug may bring a normal or closer to normal hormonal balance and that the patient may thus be enabled to carry on through the action of his own hormones, with the natural course of the disease being resumed.

With the incomplete knowledge of the effects of ACTH and similar hormones and with evidence of untoward reactions, it is quite evident that these substances cannot be recommended for routine treatment of rheumatic fever at this time. Continued studies may shed light on the etiology of rheumatic fever and furnish a new concept of disease processes.

DISCUSSION

DR. NEWCOMB, Winnetka: I should like to ask Dr. Elghammer whether the results are better if ACTH is given as soon as the disease is diagnosed or within the first week or if it is better to wait until the third week.

DR. ELGHAMMER: Our experience has been entirely with recurrent and active disease with marked carditis. I do not think we are ready to treat rheumatic fever in the early stages with ACTH. We hope to start such a study, but at present I have no recommendations. If I had such a case in my practice, I would not start administration of ACTH.

DR. NEWCOMB, Winnetka: This question is for Dr. McCulloch: The pediatrician and family doctor see many cases of what might be considered early mild rheumatic symptoms: malaise, anorexia, evanescent muscle and joint pains without acute polyarthritis, epistaxis, a moderate systolic murmur and elevated sedimentation rate. Is it not possible that best rewards might be obtained by proper treatment of this fairly large group of potential rheumatic patients? By proper treatment is meant complete bed rest for a few weeks or months, with use of salicylates, vitamins and so forth.

DR. MCCULLOCH: That problem is difficult to solve at the present time. I believe the description represents a patient who is more than a potential rheumatic subject, however; he is pretty well into the area of mild quiescent rheumatic activity. I agree that these measures should be used in such a case, because I have complete confidence in our ability, under good conditions, to control rheumatic fever and rheumatic heart disease. Under favorable circumstances most rheumatic subjects recover satisfactorily.

DR. GIBSON: According to the description, the patient has rheumatic fever if he has a significant systolic murmur located in the right portion of the heart. In doubtful cases one would put the child to bed and take care of him. In those cases the family should not be told that the child has rheumatic fever unless there is no longer any doubt that this is the diagnosis. I know of nothing more damaging than to put a patient to bed with the diagnosis of rheumatic fever when he does not have it.

DR. ROSENBLUM: I would not make a diagnosis on one examination, but I would keep the child under observation. There may be a systolic murmur with any fever, and certain symptoms may develop. But if while the child is under observation, symptoms continue to develop, a diagnosis may be made. I do not think one is warranted in advising bed rest until the child has been studied carefully.

QUESTION: Is it possible to tell which patients have sore throats due to group A Streptococcus without culture? Is the picture characteristic enough to be differentiated clinically, and, on that basis, for a three weeks' check-up to be made?

DR. ROSENBLUM: Certainly one cannot tell positively when one is dealing with group A Streptococcus without having a culture made. It is possible, with clinical experience, to say that the patient has a streptococcic sore throat; it presents many differentiating characteristics. I have seen many sore throats that I was sure were not which on culture proved to be due to Streptococcus. We made a good many cultures during an epidemic of Streptococcus sore throat, on the other hand, which proved some sore throats not to be due to Streptococcus.

DR. MCCULLOCH: At the American Heart Association meeting in San Francisco I heard Dr. Ramelkampf explain that if four criteria are fulfilled—if there are fever, angina in the throat, membrane on the tonsils and swollen cervical nodes—one probably does not need a culture. In the presence of these four signs it is probable that Streptococcus group A infection is present.

DR. GIBSON: From my clinical observation that is 90 per cent correct.

DR. NEWCOMB, Winnetka: A high cholesterol diet has been mentioned; I wonder if there is not some recent evidence that cholesterol may produce damage to the large blood vessels. Are we possibly getting into deep water by prescribing such a diet?

DR. ROSENBLUM: I think Katz and some others have proved that the high cholesterol diet is not as harmful as has been supposed. Coburn noted that cretins were not as subject to rheumatic fever as were hyperthyroid persons and fed them four eggs a day. Then he

did some work with a group of nurses in an epidemic of sore throats and found fewer cases of rheumatic fever.

DR. NEWCOMB, Winnetka: I brought this up because we are going to have an expert on our March program—Dr. S. Howard Armstrong of the University of Illinois.

Here is a question for Dr. Gibson: "How old was the youngest infant for whom you were able to diagnose rheumatic fever?"

DR. GIBSON: To the best of my recollection, between 18 and 20 months. I know there are reports of autopsies at which apparently Aschoff bodies were found in the heart muscles of babies much younger than that. It is rare, however, to make a clinical diagnosis for an infant younger than 1½ or two years.

Alvah L. Newcomb, M.D., *President*

Regular Meeting, Nov. 21, 1950

Smallpox Vaccination with Prolonged Vaccinia. DR. EUGENE L. SLOTKOWSKI.

The interest in this case lies in the fact that in the patient a severe primary reaction to vaccination developed. Three days after exposure to measles she received a diphtheria booster shot and a smallpox vaccination. One week after the booster shot and the vaccination had been given, measles developed, complicated by bronchopneumonia. The vaccination produced a primary reaction. The reaction at the site of vaccination continued to enlarge, and there were pain, swelling and tenderness of the left arm.

This 5½ year old Negro girl was admitted to Children's Memorial Hospital with a 3 by 3 inch (8 by 8 cm.) necrotic area involving the deltoid region of the left arm. A large blackish necrotic dry crust covered the center. The border was raised. On the edges of the ulcer and surrounding it were eight to ten vesiculopustular umbilicated lesions. The shoulder and arm were swollen to about half again normal size.

In spite of many forms of local and general therapy, the necrotic area in the left deltoid region continued to spread, involving the entire left upper extremity, and new lesions appeared on the left shoulder, back, face, right index finger and wrist. The lesions on the wrist and most of the satellite-like lesions along the periphery of the huge ulcer resembled, in many respects, lesions of a primary reaction to vaccination. The patient died approximately 3½ months after admission. Except for the skin lesions and extensive bronchopneumonia, the changes seen at autopsy were nonspecific.

Three possibilities were considered as being the cause of death: first, the vaccination site acted as a portal of entry for some infectious agent; second, there was contamination of the vaccination plus a superimposed change in the permeability of the tissues, the so-called Duran-Reynals' phenomenon, and third, the death was directly attributable to the vaccination, the patient having reacted atypically to the introduction of the vaccination virus.

Microscopic sections of the skin immediately adjacent to the necrotic areas revealed changes which were identical to those expected during the vesiculopustular stage of a primary vaccination reaction.

It was felt that immunity to the vaccinia virus failed to develop, and that the lesion continued to spread unopposed.

Gamma Globulin Studies in Tuberculosis in Children. DR. B. M. LEVIN.

The occurrence of marked changes in the blood proteins, especially in the globulin fractions, in cases of tuberculosis have been known for some time. A rise in the percentage of globulin was found regularly with increased severity of the infection.

By means of electrophoretic studies, Siebert found that the rise was chiefly due to the gamma globulin fraction. Huerga described a turbidimetric method of determining gamma globulin which corresponds very closely to the more complex electrophoretic method. With use of this simpler process, 73 children with various types of tuberculosis were studied for a period of from three to eight months. Weekly determinations of the serum gamma globulin were made in conjunction with sedimentation rates, hematocrit readings and total white and

differential cell counts. Normal standards of gamma globulin for the various age groups are considered to be the following: under 1 year of age, 0.5 Gm.; 1 to 4 years, 1.0 Gm., and above 4 years, 1.30 Gm. In all patients studied, regardless of age or treatment, there was a rise in the gamma globulin, with the highest level reached between the third and eleventh week from onset and a return to normal usually between the twelfth to twenty-sixth week. The curve thus produced was similar to those in the many clinical cases studied, with but slight variation.

It was likewise noted that the sedimentation rate followed closely the pattern of the gamma globulin levels in all uncomplicated cases of tuberculosis that terminated in complete arrest. However, in those cases in which the severity of the infection seemed overwhelming, there was dissociation of the sedimentation and gamma globulin pattern, the former rising while the latter dropped to extremely low levels. This phenomenon was noticed about two weeks prior to death and continued until death and was an indication of a poor prognosis regardless of the clinical appearance of the patient or the therapeutic measures employed.

Single determinations of the gamma globulin were of no value but were of great help when studied for some time in connection with the sedimentation test. Indirectly the extent of the pathologic lesion and the course of its activity were indicated.

Effect of the National Health Service of Great Britain on Child Care in England, Scotland and Wales. DR. HEYWORTH N. SANFORD.

This paper was published in full in the December 1950 issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN, page 921.

News and Comment

GENERAL NEWS

Specialists Certified by American Board of Pediatrics, Inc.—The following physicians were certified as specialists by the American Board of Pediatrics, Inc., after examination in New Orleans, on March 2, 3 and 4, 1951:

Elaine Louise Allen, New Orleans; Julia Baker, México, D.F., Mexico; Donald Frederic Bauman, Fullerton, Calif.; Robert J. Black, Rome, Ga.; Carl Arthur Brakel, Spokane, Wash.; George R. Branch, Dallas, Texas; Daniel Wilbern Burke Jr., Mobile, Ala.; Edwin C. Burklund, St. Paul, Minn.; Louise Holmes Burr, Oakland, Calif.; Donald E. Cassels, Chicago, Ill.; Lin Tung Chun, Honolulu, Hawaii; Bernard I. Copple, Tokyo General Hospital, % Postmaster, San Francisco, Calif.; James Hewitt Cravens, Quincy, Ill.; Robert Ralph Dew, Kalamazoo, Mich.; Ernest William Eberling, Starkville, Miss.; George Eckel Felknor, Baytown, Texas; Erwin D. Goldenberg, Fontana, Calif.; William Roy Green, Chattanooga, Tenn.; Arnold E. Hauser, Vallejo, Calif.; William Carter Hawkins, Dallas, Texas; Jim Gilbert Hendrick, Jackson, Miss.; Fontaine Sallis Hill, Memphis, Tenn.; LeRoy Edward Hoeck, Washington, D. C.; Joseph Gordon Holt Jr., Wichita Falls, Texas; William Floyd Humphreys Jr., Panama City, Fla.; Eloise Eberling Johnson, San Antonio, Texas; Frank Goulding Keller, Mobile, Ala.; George Peyton Kelly, Shreveport, La.; Frank Robert Kinberger, New Orleans; Herbert W. Korngold, Sacramento, Calif.; Joe L. Lipscomb, Amarillo, Texas; Gertrude C. Luther, Anniston, Ala; Stephen Laurence Madey, Baton Rouge, La.; Jerome S. Mark, North Hollywood, Calif.; Jack F. McKemie, Corpus Christi, Texas; Marion Smith McLellan, Galveston, Texas; A. Ziegler McPherson, Yazoo City, Miss.; Bruce Baxter Newman, Western Springs, Ill.; Georgia B. Perkins, Denver, Colo.; Guy Eugene Rader, Albuquerque, N. Mex.; Stephen Wheeler Royce, Pasadena, Calif.; Lee H. Sanders, Raleigh, N. C.; Herbert Victor Louis Sapper, Oklahoma City; Alvis Joe Scull, San Francisco; Robert David Shuttee, Enid, Okla.; Thomas Randolph Clinton Sisson, Tuckahoe, N. Y.; William Price Stepp, Memphis, Tenn.; Oscar Syme, Albuquerque, N. Mex.; Carolynn Downs Talley, New Orleans; Daniel Martin Thomas, Oak Ridge, Tenn.; John W. Thompson, Atlanta, Ga.; George Clifford Thorne, Austin, Texas; Steve H. Turnbull Jr., Memphis, Tenn.; John B. Welsh, Anderson, Ind.; Lloyd Parrish Williams, Appleton, Wis.

Specialists Certified by American Board of Pediatrics, Inc.—The following physicians were certified by the American Board of Pediatrics, Inc., after examinations held in Cincinnati on March 30 and 31 and April 1, 1951: Robert Anderson Aldrich, Rochester, Minn.; Harriet Hegar Bates, Dallas, Texas; Blair Everett Batson, Nashville, Tenn.; Jefferson D. Beale Jr., Danville, Va.; Joseph A. Bertucci, Chicago; Clark William Biedel, Bremerton, Wash.; Armistead Page Booker, Charlottesville, Va.; I. Blanche Bourne, Washington, D. C.; Harben Jay Boutourline-Young, Weston, Mass.; Wendell E. Brown, Indianapolis; Charles H. Buchert, Middletown, Ohio; Anthony R. Ceresko, Detroit; Hugh Gambel Clark, Washington, D. C.; Joseph E. Coleman, Evansville, Ind.; Thomas L. Duffy, Great Lakes, Ill.; Gustaf Walter Erickson Jr., South Bend, Ind.; Roy Francis Garrison, Kansas City, Mo.; George S. George, Chicago; Benjamin Pierce Gilbert, Gainesville, Ga.; Bruce Douglas Graham, Ann Arbor, Mich.; Frederick D. Haffner, Cincinnati; Albert Moore Hand, Texarkana, Texas; Arvin T. Henderson, San Diego, Calif.; Frank VerNooy Hertzog, Elmira, N. Y.; Edmond Richard Hess, Chicago; Oliver Adolph Horak, Lima, Ohio; Edward Kenneth Isaacson, Chicago; Frank K. Johnson, Beloit, Wis.; D. Joseph Judge, Rochester, Minn.; Peter Kalick, Sherman Oaks, Calif.; Philip J. Laux, Birmingham, Mich.; Charles Upton Lowe, Minneapolis; Frederick J. Martin, Rochester, N. Y.; Daniel Bernard McIlvoy Jr., Bowling Green, Ky.; J. Schuler McKinney, El Dorado, Ark.; Frederic P. Moore, II., Richmond, Va.; Lloyd Stanley Nelson, Minneapolis; Robert B. Olney, Los Angeles; Leslie Pensler, Detroit; Mario Peter Pestillo, Syracuse, N. Y.;

Francis L. Richardson, Philadelphia; Howard W. Ripy, Lexington, Ky.; Charles W. Rogers, Winona, Minn.; Robert Smedley Rothwell, Salt Lake City; James M. San, Tampa, Fla.; Robert M. Scott, Sacramento, Calif.; Theodore S. Smith, Minneapolis; Morris Tandeta, Castro Valley, Calif.; Natalia Murphy Tanner, Chicago; Lansing Stephen Thorne, Cincinnati; Richard D. Turin, Brooklyn; George F. Walliker Jr., Portland, Ore.; Sydney A. Warren, Toronto, Ont., Canada; James Donald Watson, Colorado Springs. Colo.; Frederick B. Wilkes, Buffalo.

ANNOUNCEMENTS

M & R Pediatric Research Conferences.—On Nov. 16, 1950 the first of the M & R Pediatric Research Conferences was held under the chairmanship of Allan M. Butler at the Burnham Memorial Hospital for Children, Massachusetts General Hospital, Boston. The subject of this first conference was the role of vitamin B_{12}, folic acid, citrovorum factor and vitamin C in the megaloblastic anemias of infancy (to be published by *The Journal of the American Medical Association*). The second conference, on retrolental fibroplasia, was held on April 28 at New York University under the chairmanship of L. Emmett Holt Jr.

M & R Dietetic Laboratories are to be congratulated for the foresight and generosity that make possible the establishment and continuation of such conferences. Their contribution to pediatrics should be great.

Twenty-First Italian Congress of Pediatrics.—The Twenty-First Italian Congress of Pediatrics, announced by the Società Italiana di Pediatria and organized by Professor Bentivoglio, Director of the Pediatric Clinic of the University of Padua, will be held in Venice, at the Lido (Palazzo del Cinema), Sept. 16, 17, 18 and 19, 1951. The following subjects will be discussed: (1) allergic diseases in infancy, including etiology, pathogenesis and clinical pictures (speaker: Prof. G. Guassardo); (2) clinical forms of dysvitaminosis B in infants (speaker: Prof. G. Frontali), and (3) hemorrhage in the newborn (speaker: Prof. P. Brusa, with the cooperation of Prof. A. Ponche and Prof. V. Migliori). The secretariat of the organizing committee is located at the Pediatric Clinic of the University of Padua, via Giustiniani, 6, Milan, Italy.

Third Pan American Congress of Pediatrics.—The Third Pan American Congress of Pediatrics will be held in Montevideo, Uruguay, Dec. 5, 6, 7 and 8, 1951. The subjects to be discussed will be rheumatic fever, blood diseases of hemorrhagic tendency, surgical treatment of congenital malformations, parasitic diseases of social importance in the child, teaching of pediatrics and mental hygiene and neurosis in infancy. During the congress there will be scientific, artistic and industrial expositions. Further information may be secured from the Secretarial Office of the Congress, Av. 18 de Julio 1246, Montevideo, Uruguay.

Pediatric Conference at the University of California School of Medicine.—The University of California School of Medicine will hold a pediatric conference June 18 through 22, 1951. The guest lecturer will be Dr. Lawson Wilkins of Johns Hopkins University, and the whole course will be under the direction of Dr. William C. Deamer, Professor of Pediatrics at the University of California School of Medicine.

Anyone wishing to attend should give the medical school attended and the year of graduation and enclose a check for $50.00 made out to The Regents of the University of California.

Pediatric Postgraduate Course.—A pediatric postgraduate course will be given at the University of Arkansas School of Medicine, Little Rock, Ark., by the pediatric department on May 14 and 15, 1951. This is a course mainly for general practitioners. Dr. Myron E. Wegman of Louisiana State University Medical School, New Orleans, and Dr. Gilbert B. Forbes of Southwestern Medical School, Dallas, Texas, will be the guest speakers. No fee will be charged for this course. All interested physicians, nurses and public health workers are invited to attend.

Coming Examinations to be Held by the American Board of Pediatrics, Inc.—The American Board of Pediatrics, Inc. will hold oral examinations on May 5, 6 and 7 in

Atlantic City, N. J., and on June 8, 9 and 10 in Detroit. This examination session replaces the one originally scheduled for Cleveland in June.

NOTICES

The National Home for Jewish Children at Denver.—Since 1940 the National Home for Jewish Children of Denver has carried on a physical and mental hygiene program for the rehabilitation of asthmatic children and those suffering from other allergic disorders. The home has facilities for 140 children, of whom 85 per cent fall in this category. They come from all over the country through referrals from physicians, family social service agencies and private sources. The National Home for Jewish Children is a nonprofit organization, supported by private philanthropy. It does not charge for its services. Applications may be made at the New York office of the home at 1407 Broadway, New York 18, or the Los Angeles office, 3932 Wilshire Blvd., Los Angeles, or by writing directly to the home at 3447 West Nineteenth Avenue, Denver 4, Colo.

PERSONAL

Appointment for Dr. Katherine Bain.—On April 3, Dr. Katherine Bain was sworn in as chief of the Medical Department of the Childrens Bureau, Federal Security Agency. She has been employed in the Childrens Bureau for some time and is generally respected and liked.

Book Reviews

Clarke School Studies Concerning the Heredity of Deafness, Monograph 1: Pedigree Data. By Louise A. Hopkins, M.S., and Ruth P. Guilder, M.D. Complimentary distribution. Pp. 162, with numerous graphs. Clarke School for the Deaf, Northampton, Mass., 1949.

This booklet consists chiefly of the pedigree data of nearly 300 pupils observed at the Clark School for the Deaf in Northampton, Mass., between 1930 and 1940. Included with these data are condensed histories and audiogram records of all relatives of the deaf pupils about whom information could be obtained. The volume is therefore chiefly made up of pedigree charts, with explanatory footnotes in cases of deafness which were thought to be congenital and hereditary.

The summary of this huge collection of data is, however, of extreme interest. We learn that the deaf children were no more susceptible to middle ear infections than their hearing brothers or sisters, a point which casts considerable doubt on the frequent assertions of parents that their child's deafness is due to middle ear disease. Deafness in children tended to occur at random through the family, indicating that order in family had no particular influence in producing congenital defects. The children with hereditary deafness were not born of mothers who were older than the average mother. It appeared that the deaf children at the Clarke School were of foreign parentage in excess of the proportion of foreign parents in the population of the state. It was thought that this may have been due to intermarriage among those whose relationship to one another was unknown to them, thus bringing together recessive defects. After an examination of numerous extraneous factors which have been invoked to explain the occurrence of other congenital defects, the authors found none which seemed to have been contributing factors in causing deafness. The basis for the appearance of deafness in congenital form is a factor for deafness which is inherited. In other words, congenitally deaf children do not inherit factors for normal auditory function. a lack which results in the condition we call deafness.

This work can be highly recommended to those interested in genetics, otology and aural rehabilitation. It represents a painstaking and significant research effort.

Malnutrition and Starvation in Western Netherlands, September 1944-July 1945. Compiled by the American Public Health Service Group assigned to SHAEF and distributed without charge by the United States Public Health Service. Price, not given. Vol. 1, pp. 187; vol. 2, appendixes, pp. 299. General State Printing Office, The Hague, Netherlands, 1948.

These two sober and dispassionate volumes contain official accounts of the "hunger winter" of 1944-1945, its effects on the lives and health of Dutch civilians and the lessons learned during its alleviation. The contributors are, for the most part, medical and public health experts. Meeting in liberated Belgium and realizing that the liberation of the Western Netherlands, when it came, would bring the immediate problem of dealing with the famine status inflicted by the Nazis, these experts and their military associates were faced with "a deplorable paucity of knowledge regarding the treatment of individuals suffering from grave starvation." Therefore, while attempting the wisest possible preparation for such therapy on a mass scale, they also proposed to study as carefully as circumstances allowed the pathology of starvation and the most effective methods of treatment.

Planning was difficult. The severity of the situation could not be predicted. The date and the speed of liberation could only be guessed. It was assumed that "feeding-teams" could

deal with one local situation before passing on to the next, as the occupying forces capitulated in city after city. It was also assumed that many starved people would be unable to swallow and that the digestion of practically all would be so impaired as to require predigested food. A large supply of materials and apparatus for intravenous and nasal tube feeding was therefore assembled, and much time was given to training about a thousand technical personnel in its use.

Actually, when liberation came on May 5, 1945, it was complete. The needs of all the great cities—Amsterdam, Rotterdam, The Hague and others—had to be met at once, to the great detriment of arrangements for careful clinical and laboratory surveys. Considerable inequalities of dietary conditions were met in cities almost adjoining one another, or even in the same city, and although some 10,000 deaths from starvation had occurred during the preceding few months, it was not always easy to find the persons most in need of relief, the majority of whom were the aged and the indigent.

Faced with these problems and others of a kaleidoscopically shifting nature, it is remarkable that so much valuable data were secured. Among the outstanding observations was the fact that intravenous and tube feeding with protein hydrolysates were only of apparent value in the less common cases of far advanced cachexia; simple diets of 3,200 calories with 300 Gm. of protein a day were more effective for the starvation ordinarily encountered. The situation was one of mass undernutrition rather than selective malnutrition, so that vitamin deficiencies were signally lacking. Infants and children, with preferential status in rationing, were relatively better off than adults, especially the aged. Most mothers were able to nurse their infants. "Famine-edema," except for underweight, the commonest specific nutritional symptom at all ages, was presumably related to capillary permeability rather than hypoproteinemia. Numerous other observations, comprising clinical and biochemical data of all sorts, with photographs and tables, will be found in these volumes. Though the data are necessarily somewhat fragmentary, they offer essential information for the treatment of starvation. The objective attitude of these reports has left no room for editorial comment on the anguish and stoicism of millions of people, but the reader will have no difficulty in appraising these for himself.

Public Health Is People. By Ethel Ginsburg. Price, $1.75. Pp. 241. Commonwealth Fund, Division of Publications, 41 E. 57th St., New York 22, 1950.

"Public Health Is People" is a detailed account, much of it verbatim, of an institute on mental health in the field of public health, which was held in Berkeley, Calif., in July 1948 under the joint sponsorship of the California State Department of Public Health and the Commonwealth Fund.

The purpose of the institute was to bring about or arrive at a better understanding of what a health department might do in the field of mental health. From this purpose stemmed the discussion of many phases, developments and technics occurring in the process of organizing and carrying on a mental health program. Throughout these discussions emphasis was placed on the technics within the scope of the public health worker which are advisable for use.

The step by step progress of the institute is described clearly in this report. Psychiatrists served as the faculty and the public health worker became the student in working out the problems in mental health which could be partially solved by public health employees. It is pointed out that at the beginning of the institute a great deal of fear, tension and anxiety were manifested in both faculty and student groups, but after threshing out together principles, policies and purposes of the conference, the position of each was clarified and each group learned from the other. Long before the end of the report the reader is conscious of a mutual learning situation and a mutual understanding of the potentialities of a community mental health program sponsored by a local health department.

In this report new concepts point out the importance of good interpersonal relations in all phases of public health work: administration, intrastaff relations, community relations and clinical services. This book is an excellent guide in developing any community mental health program. First, it can help the public health worker to realize that through his everyday

activities he can promote mental health within the community. Second, it offers leads and suggestions to those who wish to incorporate mental health concepts in staff development programs. Third, it reaffirms the conviction that this sort of training should be available to students in professional schools for the training of health and welfare workers. Most important, this book points out that a mental health program is the concern of the entire community and depends for its success on the combined efforts of its citizens, who can be motivated to a great extent by the health department personnel.

Het rubella-probleem in het licht van Nederlandse ervaringen. By A. Elizabeth H. M. Kamerbeek, M.D. Publication of the Institute of Preventive Medicine. Price, 7.00 florins. Pp. 212, with 36 tables. H. E. Stenfert Kroese's Uitg.-Mij. N. V., Breestraat 14, Leiden, Netherlands, 1949.

In this monograph is presented an attempt to evaluate, verify or disprove the theories and reports on the problem of rubella in pregnancy.

The author reviews the Australian, English and American literature and presents the Netherlands approach. On the one hand, German measles occurred significantly oftener during the pregnancy of mothers of deaf-mute children than during those of mothers of normal children born in the same year. On the other hand, they were unable to infer the chance of defective offspring in proved cases, partly because the duration of pregnancy is such a vital factor. Under two months gestation enhances the danger tremendously.

The verification of the diagnosis is reviewed, including blood studies in which the elevation of stab forms and leukopenia, as reported by MacBryde and Charles, are emphasized.

General studies of significance show that women in populated and sparsely populated areas vary in susceptibility to rubella.

The use of convalescent serum is advocated on exposure of a pregnant woman to rubella. Because the incidence of susceptibility was low, its benefit could not be proved statistically.

Review is made of virus studies with a view to immunizations.

This handbook is a thorough treatise on the impact of this relatively new phase of medicine on the situation in the Netherlands.

Mitchell-Nelson Textbook of Pediatrics. Fifth edition. Edited by Waldo E. Nelson, M.D. Price, $12.50. Pp. 1658, with 426 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1950.

The new edition of Nelson's text appears five years after his first revision of Mitchell's textbook. The extensive changes are notable in the size of the book, which is now 300 pages larger than the previous edition. The number of contributors has increased from 49 to 63.

Many sections are new or completely rewritten. Especially well done are those on growth and development, congenital malformations, parenteral fluid therapy, congenital heart disease, inborn errors of metabolism, infection, immunity and allergy. The section on mental growth and development has been revised by Dr. Milton J. E. Senn, who has included a new section on psychological aspects of adolescence. Increased attention is given to hearing defects and the eye. Surgical treatment of congenital heart disease is presented by Willis Potts.

Material on pediatric anesthesia, while included, is sketchy and the subject could well be discussed in more detail. While an excellent section is included on orthopedic pediatrics, a similar discussion of surgical pediatrics would be a valuable addition. Another omitted topic that should be included in a book of this stature is pediatric pathology, a subject as yet given too little consideration by pathologists and pediatricians both.

The previous edition of this book was a great success. This new edition will probably be the most popular text in the field. Its size is indicative of the broadening of the scope of pediatrics. Despite its bulk, articles are uniformly easy to read and show the effect of careful editing. It is a book which should be in the library of everyone concerned with the treatment of children.

Medical Clinics on Bone Diseases: A Text and Atlas. By Isidore Snapper, M.D. Second edition, revised and enlarged. Price, $20. Pp. 308, with 264 illustrations on 64 plates (234 illustrations are true photographic prints). Interscience Publishers, Inc., 215 4th Ave., New York 3, 1949.

Snapper was one of the first to demonstrate the relationship between generalized fibrocystic disease of the bones (often called von Recklinghausen's disease) and parathyroid adenoma. For more than twenty years since this initial contribution to the metabolic diseases of the human skeleton, Snapper has constantly brought the light of truth to bear on many other diseases which affect in a general way the human skeleton; he has helped clarify understanding of their causes, and, when possible, the means of controlling them.

In the first edition all the commoner bone diseases were presented, with emphasis on the systemic manifestations. In the second edition, the chapter on hyperparathyroidism is subdivided into four parts. New chapters on osteoporosis and osteoporosis circumscripta cranii, osteitis fibrosa disseminata, leontiasis ossea, neurofibromatosis of the bones, lymphosarcoma, Hodgkin's disease and hemolytic anemias are added. Other chapters are enlarged or subdivided to clarify the differential picture between conditions which from the standpoint of the roentgenogram, or earlier and less complete clinical investigations, appear to be related.

The book is large, the printing unusually clear and easy to read, and both the photomicrographic and the roentgenographic illustrations are of excellent quality and detail. Those who are interested in internal medicine, endocrinology, orthopedic surgery or laboratory research in calcium and phosphorus metabolism cannot afford to be without access to this volume as a book of reference.

El tratamiento sintomático y dietético de las diarreas agudas del lactante. By Dr. Pastor Oropeza. No price given. Pp. 51, with 4 tables. Editorial Bellas Artes, Caracas, Venezuela, 1949.

This little book is written by Dr. Pastor Oropeza, professor of pediatrics of the Central University of Venezuela and Chief of the Maternal and Infant Division of the Ministry of Health. It is primarily intended for the physicians of Venezuela as a help in the treatment of diarrheas of infancy. These diseases are the commonest cause of death of infants in Venezuela and result in more than one third of all the deaths in this age group.

Dr. Oropeza reviews the literature on the etiology and classification of infantile diarrheas, describes their diagnosis and treatment and writes from a practical standpoint on the best way these conditions may be controlled. The brochure, written in Spanish, is interesting and instructive.

Krämpfe im Kindersalter. By Hans Zellweger. Part I in *Helvetica Paediatrica Acta* supplement V, volume 3, 1948. Price, 18 Swiss francs. Pp. 195, with 28 illustrations. Benne Schwabe & Co., Klosterberg 27, Basel, Switzerland, 1948.

This is a complete and thorough review of the subject well sprinkled with case reports. The author presents the various theories of the causation of convulsions. He emphasizes that a convulsion is only a symptom. He presents the vasomotor and the water-retention theories and the significance of hypoglycemia and of the acid-base balance.

Chapter 1 reviews the respiratory affect convulsion, and there is an excellent discussion on heredity and the importance of the inherited constitutional type.

Chapter 2 deals with convulsions due to fever or infection. These are well described and explained. There is a thorough discussion of the blood, urine and spinal fluid changes. The influence of heredity is again emphasized in these fever convulsions.

Chapter 3 discusses so-called salaam or nodding spasms and their relationship to convulsions.

The serious criticism which must be made of this book is the absence of electroencephalographic studies. It is not possible to make a complete and thorough study of convulsions today without including electroencephalography.

Anyone who doubts or questions the influence of heredity in epilepsy or in the general convulsive disorders would do well to review this book. The serious prognosis of so-called fever convulsions is also well established. Perhaps too much emphasis is placed on minor variations from normal in the blood chemistry and also in the shape and size of the sella turcica on roentgenogram.

The Care of Your Child. By Béla Schick, M.D., and William Rosenson, M.D. Price, $0.25. Pp. 288. Dell Publishing Company, New York, 1949.

This is a pocket-sized edition of a book on child care. As would be expected from the widely known reputation of the authors, its contents are authoritative and reflect the present day point of view. A middle of the road course is taken between the former rigid routines and the modern trend toward the abandonment of all schedules and disciplines.

The book is conveniently divided into four parts. The first part deals with the prenatal period and covers such subjects as the Rh factor, rubella in pregnancy and the rooming-in arrangement. Other sections take up infancy, the preschool child and the disorders and diseases of childhood. Most parents will find chapter 13 on "Child Guidance and Behavior Problems" particularly useful.

It is the reviewer's impression that this is a carefully prepared, sound book, and one which will solve most of the problems encountered by parents.

A Miniature Textbook of Feeblemindedness. By Leo Kanner, M.D. Price, $1.25. Pp. 33, with no illustrations. Child Care Publications, New York, 1949.

In the author's opinion feebleminded persons should be classified into (1) the absolute, pathologically irreversible feebleminded; (2) those relatively trainable culturally, and (3) the apparently feebleminded or pseudofeebleminded. The first require custodial management. The second require adjustment and guidance, and the third require adequate diagnosis and treatment of those handicaps which have prevented existing potentialities from coming to full fruition.

There is still room for improvement of educational and vocational facilities everywhere. The specialists in the training of mentally deficient persons should have an opportunity to prepare themselves adequately for a task which can be thrilling and full of rewards.

Mongolism and Cretinism. By Clemens E. Benda, M.D. Second edition, revised. Price, $7. Pp. 316, with 103 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1949.

The second edition of this book has been revised so far as new approach is concerned, especially in regard to the relationship of mongolism to maternal condition. Here the author presents new facts to substantiate his opinion that mongolism develops in the fetus under a constellation of adverse factors which operate in the maternal organism and deprive the growing fetus of proper nutritional environment. He expresses his belief that studies of latent hypothryoidism, hypogonadism and hypopituitarism may reveal the condition prenatally.

The chapter on principles of treatment has been thoroughly revised. The author outlines his principles of treatment with thyroid, pituitary extract and other hormones, glutamic acid and education. He states that "under present

conditions, treatment cannot restore full intelligence; the results of careful treatment carried out over several years lie between normal and the level usually reached by untreated patients."

The book is well written and excellently printed and should be of interest to everyone concerned with this subject.

Healthy Babies Are Happy Babies: A Complete Handbook for Modern Mothers. By Josephine Hemenway Kenyon, M.D., and Ruth Kenyon Russell, M.D. Fourth edition, revised. Price, $2.50. Pp. 310. Little, Brown & Company, 34 Beacon St., Boston 6, 1949.

There is nothing particularly unusual about this book. The material is in keeping with modern thinking about the care and management of infants and young children. Parents will find the advice given to be sound and reliable and expressed in simple terms easily understood. Answers will be found to most of the questions likely to arise in the rearing of normal children. Throughout the book care has been taken to advise professional consultation for all but the simplest difficulties. Physicians may safely recommend "Healthy Babies Are Happy Babies" to their patients.

El problema de la alimentación media infantil. By Carlos Sáenz Herrera, M.D. No price given. Pp. 11, with 3 tables. Imprenta Nacional, San José, Costa Rica, 1949.

This is a study, written in Spanish, of the nutrition of Costa Rican children. The author gives a summary of the diets in various parts of Costa Rica with food values and costs. The nutritional problem is economic and educational. Fifty per cent of the instances of nutritional deficiencies come from homes with very low incomes. The main deficiency is in protein. The author is of the opinion that this may be overcome by adding soy bean protein, which is adequate in content and cheap in price. Most frequently the disturbances come in the group 1 to 4 years of age and are due to lack of proper food and parasitic infection.

This is an interesting study for anyone interested in diets of children in this area. The study is well done.

Handbook of Medical Management. By Milton Chatton, M.D., Sheldon Margen, M.D., and Henry D. Brainerd, M.D. First edition. Price, $3. Pp. 476. University Medical Publishers, Palo Alto, Calif.

This is an excellent volume containing a wealth of information in compact form on the management of disease.

The first chapter, on general aspects of medical management, discusses such problems as activity status, positions for bed patients, rules for home management and other features not usually emphasized in books on therapeutics. Many useful tables are scattered throughout the volume enabling the authors to present a maximum amount of information in a minimum of space.

As in any handbook, in which brevity is of prime importance, certain inadequacies become apparent. Treatment is presented in outline form; hence little discussion is available on questionable problems of treatment. Only one paragraph is presented on the management of multiple sclerosis. The use of histamine in the treatment of certain types of headache is not even mentioned. The treatment of thyroid crisis is dismissed with one short paragraph emphasizing that its management is symptomatic. The use of diethylstilbestrol in the treatment of mumps orchitis is not mentioned. The chapter on acute poliomyelitis states that "patients with involvement of the respiratory center are generally not helped by the use of the respirator."

These criticisms are not made to detract from the value of the volume but merely to draw attention to the fact that it is difficult to present such a vast amount of material in outline form without, in some cases, having brevity assume dominance over completeness. There is no bibliography.

In general, this handbook should be an excellent quick reference for the busy practitioner or as a summary on treatment for the student. It should not be expected to supplant the more comprehensive books on medical therapeutics.

Golden Jubilee World Tribute to Dr. Sidney V. Haas. By the Committee for the Golden Jubilee Tribute to Sidney V. Haas. No price given; complimentary distribution. Pp. 38, with 8 photographs. New York, 1949.

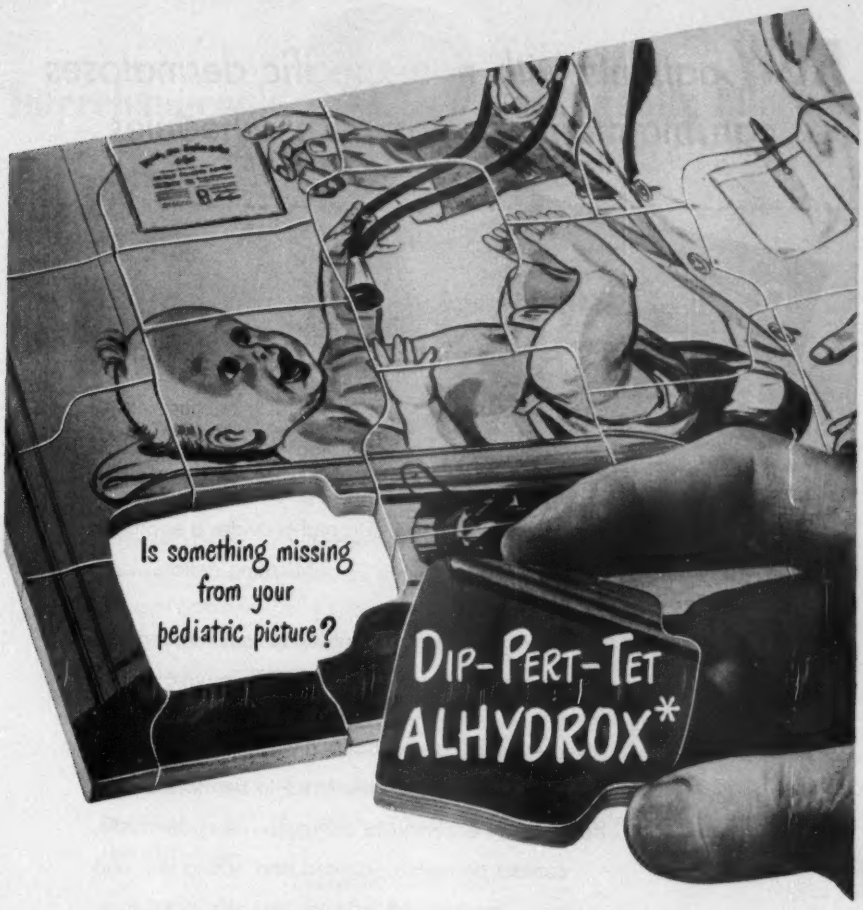
This is a fine tribute to Dr. Sidney V. Haas, of New York, whose work is so well known.

My Get-Well Trip. By Constance B. Crail. No charge. Pp. 25, with illustrations by Munro Leaf. National Foundation for Infantile Paralysis, Inc., 120 Broadway, New York 5, 1949.

This little book is meant to be given to hospitalized children who are being treated for poliomyelitis. It should make life easier for these little crippled patients and it certainly should be attractive to them. The illustrations are well drawn, almost as though by the children themselves, and the text is in large print. On the whole, it is altogether a delightful innovation.

Nursing: An Art and a Science. Third edition. By Margaret A. Tracy. Price, $4. Pp. 625, with 183 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1949.

This is the third edition of a standard nursing textbook. It is concerned primarily with nursing technic and procedures. It appears to be complete in its coverage of procedures and is well written and well illustrated. The book can be recommended for the beginning student.



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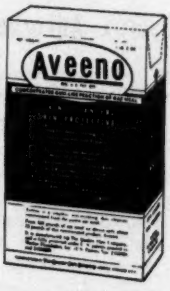

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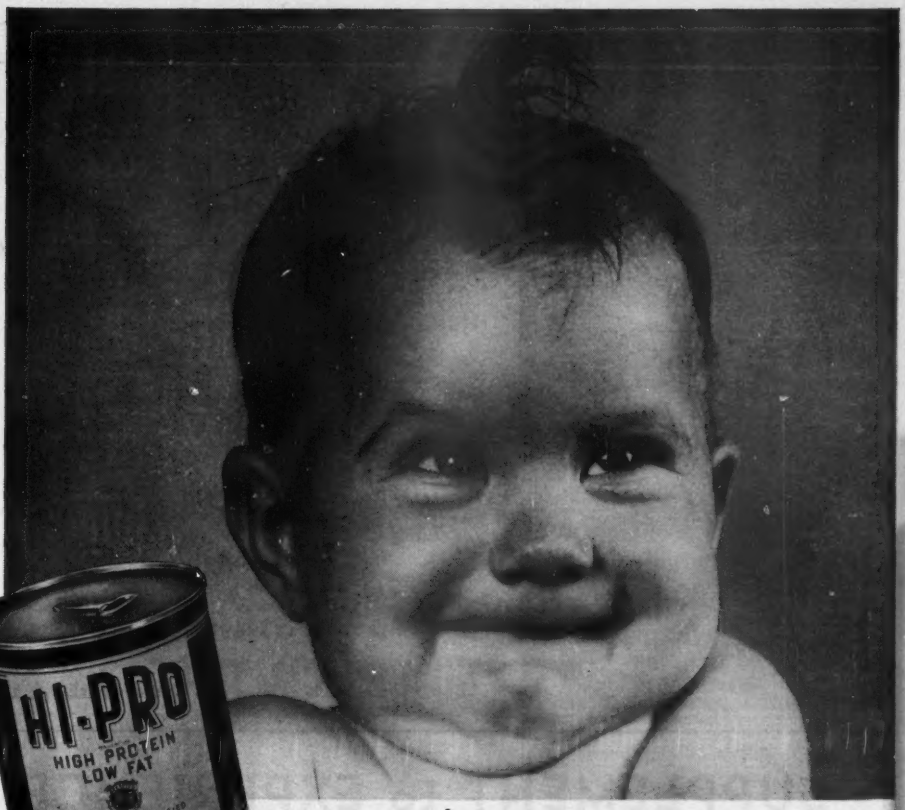

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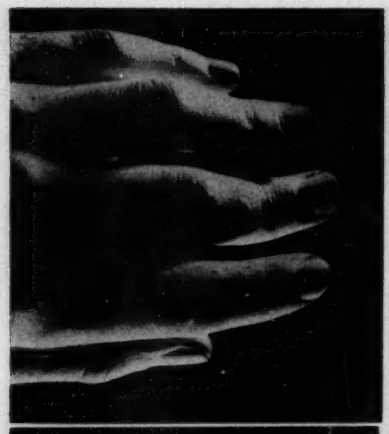

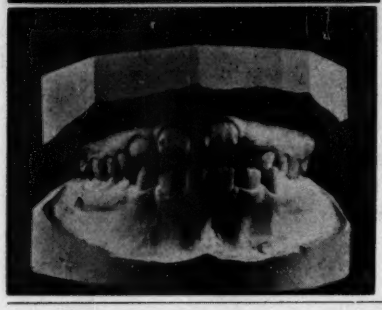

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2. *Rohr, J. H., and Colwell, A. R., Proc. Amer. Diabetes Assn. 8:37, 1948.*

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